Review Article

A Global Perspective of the Prospects and Challenges of an Awaiting Revolution of Biosimilars

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Abstract

Therapeutics derived through application of modern biotechnology has become an essential component of contemporary pharmacology and clinical medicine. Biopharmaceuticals have given an unprecedented edge to humanity to treat many formidable diseases. It has been anticipated that biotechnological medicines will occupy 50% share of pharmaceutical market by next decade. The first ever biotech drug came into use by the advent of recombinant insulin in early 80’s. Since then many biologics including recombinant human protein and monoclonal antibodies followed that changed the world of therapeutics. All these came through years and years of intensive research and at the cost of huge investments. Now we are passing through a time when some of the biologics have lost patent protection and many are moving towards it. “Patent Cliff” is a well noticed term nowadays in biopharmaceutical industry that opened the scope for “biosimilars” entry into therapeutic market. This simply means that the expiry of patent protection for many original biopharmaceuticals or biologics has led to the development of newer versions of original products. These similar products are called “biosimilars” or “non-original biologics”. Biosimilars are also innovative biotechnology medicines but copy the original technology to obtain a therapeutic what is similar to the original one. However, there might be differences on a protein level depending on the biological process of manufacturing. Biosimilars represent the newer class of biotech medicinal products that have been anticipated to have significant impact on therapeutics market. Biosimilars development is currently one of the fastest growing areas in biopharmaceuticals industry because of incumbent patent expiry of top 12 best-selling biologics. In June 2013, world’s first biosimilar of infliximab, Remsima® (CT-P13) developed by Celltrion, was approved by the Committee for Medicinal Products for Human Use (CHMP) of European Medicine Agency (EMA). Many more biosimilars are in the pipeline and some are awaiting approval. Biosimilar approval has evoked a competition in global market targeting the blockbuster biologics. The underlying reason is that biosimilars will dramatically reduce the cost of treatments where biologics are predominating. Moreover, a recent advance in technology in biopharmaceutical industry allows showing similarity between
originator and biosimilar product. Although biosimilars are emerging in the market and their market share is increasing although there are many issues raising the concerns such as safety, immunogenicity, regulatory processes, pharmacovigilance, automatic substitution, naming and labelling rules. Recent evidences have been able to demonstrate quality, efficacy, and safety of biosimilars whereas a lack of interchangeability and international standards has to be addressed. Here we provide a brief overview of biosimilars development, its increasing uses and market value as well as opportunities for emerging pharmaceutical industries.

**Keywords:** Biotechnological medicines, Biopharmaceuticals, Biologics, Biosimilars, Immunogenicity, Monoclonal Antibodies (mAb)

**KEY TAKEAWAYS**

- It is solely the price consideration that is pushing the governments in developed countries for lower prices for biologics. In parallel, reduced costs are attracting emerging markets as well. In combination, both the markets are driving the biological market of “off-patent” biologics towards biosimilars.

- Developing a biosimilar is a complex process and requires significant investments to go through manufacturing, regulation, sales, marketing and assessments.

- Less stringent regulation in pharmerging markets is alluring MNCs to develop biosimilars to provide access to therapy in affordable costs. This is also the underlying fact for rapidly evolving a number of local payers in the market. These local players can potentially move from localization to globalization.

- Roadmap shown by EMA is considered as “gold standard “and FDA also followed their footsteps. Therefore, a competition is going on which is favouring biosimilars over biologics in some extent.

- Successful development of biosimilars for 12 blockbuster biologics that will lose patent protection will bring next wave of biosimilars. It will likely to have greater impact on market to shift more towards biosimilars.

- Taking the advantage of biosimilars growth and market requires our capacity building in first place. Government must take a role in here to encourage local pharmaceutical companies and novel enterprises to build-up their capacities in order to take the challenge of future therapeutics market.

- Emerging nations have adopted different strategies to develop their capacities to capture global biosimilar market share. Therefore, it is well expected that future biosimilar market will be very competitive. It seems that local players might get advantages over global players in market race.

- Large MNCs has already created a market but new players will have to create it. Driven by the competition and keep the market, partnership between global and local players might become a potential business model in future biosimilar industry.
INTRODUCTION
Translational research is a bi-directional process in research where knowledge and ideas are shared by scientific and clinical disciplines. The American Physiological Society (APS) has defined translational research as “the transfer of knowledge gained from basic research to new and improved methods of preventing, diagnosing, or treating disease, as well as the transfer of clinical insights into hypotheses that can be tested and validated in the basic research laboratory”. The past decade has witnessed an unprecedented acceleration in the pace of translational research in biology. The landscape of research is very pretty dynamic due to biotechnological revolutions that ultimately modified the concepts and scopes of treatment. Development of sophisticated molecular methods has not only improved the specificity of molecular diagnosis and therapy, rather permits the direct application of genomic profiling for our understanding as well as the choice of targeted molecular therapy. Expanded use of immunological interventions significantly widened the range of diseases amenable to treat more efficiently. Advanced molecular diagnostic tools allowed identification of diseases based on molecular characteristics, rather than traditional ways. This paradigm shift ultimately led effective targeted therapeutic interventions at much earlier stages of disease. “Biopharmaceuticals” or “Biologics” are at the heart of current treatment regimes resulting from translation of basic laboratory research in application. Translational immunology is at the core of this discipline.

The world of biomedical sciences has entered into a new era of “Biopharmaceuticals” or “Biologics” long ago. Biologics simply refers to any medicinal product manufactured in or extracted from biological sources or semi-synthesized from them. Biologics came in use before the advent of modern molecular biotechnology derived from animals and humans such as whole blood, blood components, plasma, organs and tissue transplants etc. There are some biologics such as insulin that were previously extracted from animals, but nowadays produced by recombinant DNA technology in microbial host. Emergence of modern biologics started with the advent of recombinant human insulin produced using the E. coli expression system by Genetech and Eli Lilly back in 1982. By and large, contemporary biologics are generated by biological processes involving recombinant DNA that includes signalling protein, growth hormones, monoclonal and polyclonal antibodies, stem cells, tissue products, vaccines and fusion peptides etc. Cutting edge biomolecular research on large biomolecules or biologics and advanced analytical methods enabled us to deal with difficult challenges in diagnosis and therapy. Over last few decades, the biology of protein, immunology, pathology and genetics have evolved so rapidly that a transformation is clearly seen in diagnostics and therapeutic industry. These developments let a wide variety of systemic and infectious diseases more manageable and curable. Currently there are over 900 biologics in the pipeline, many of which are awaiting FDA approvals (Alam, 2015).

In 1975 Georges Köhler and César Milstein successfully fused myeloma cell lines with B cells to produce immortalize hybridomas that made monoclonal antibodies to known antigens. In 1988, Greg Winter pioneered the techniques to humanize monoclonal antibodies and revolutionised the biotech industry. Since its inception has been a very consistent growth in the monoclonal therapeutics market. A third of all new drugs are monoclonal antibodies. The monoclonals and vaccines make up the biggest two categories followed by recombinants and cell therapy. There are over 30 therapeutic monoclonals are available in the US market for treating cancer, cardiovascular diseases, inflammatory diseases, transplant rejection, rheumatoid arthritis, macular degeneration, multiple sclerosis, viral infection and autoimmune diseases. The market share in the US was around $15 billion in 2005 which rose to an
estimated $21 billion in 2011. This exemplifies the fact that biologics are a cornerstone of therapy for a wide spectrum of disorders nowadays. The interesting fact is, the patents for a number of widely used biologics have expired or are approaching expiration. This opportunity of patent expirations has given the scope for biosimilar emergence (Alam & Muller, 2012).

**TERMINOLOGIES OF BIOTECHNOLOGY MEDICINES**

A chaos and confusion exists regarding the biopharmaceutical terminology across the continents and it has been going on since their advent. The underlying fact is the word “Biopharmaceutical” encompasses a wide variety of views, paradigms, and definitions in terms of products, technologies, scientific environment or the industry. The broad biotech definition within the US context defines biopharmaceuticals as pharmaceutical products that are inherently biological in nature due to their manufacture using biotechnology or live organisms. But in European context where “new biotechnology” view predominantly isolates the term to genetically engineered products i.e. recombinant proteins and monoclonal antibodies. Instead of biopharmaceuticals, “Biologics” or “Biological Drugs” are widely used among European nations. Terminology is critically important for biotechnology drug industry because this is central to related classification and nomenclature of products. More importantly, the nomenclature used generally harbours a uniform framework for communication, understanding and conceptual paradigm for many marketing, clinical application and regulatory management (Rader, 2007).

The common terms used for different types of biotechnology drugs are biologics, biogenerics, biosimilars, follow-on biologics, follow-on proteins, biocomparables, biobetters, off-patent or multisource biopharmaceuticals etc. It is utmost important to have idea about who is who in biopharmaceutical glossary. Here we summarize some definitions perceived by FDA and the EMA. **Biopharmaceutical** is an active biological agent that is biological in nature and manufactured using biotechnology in a living organism or host. An **innovator** refers to an original product or the first entrant to receive approval. These products come through original and extensive research and development (R&D) and full phase III type safety and efficacy testing. **Biologic(s)** generally refers to all biopharmaceuticals regulated as drugs by the FDA although the official definition is often complex. The term was coined in early days of the modern molecular medicine and therefore sometimes refers to products developed through recombinant DNA technology. **Biological product** is an official synonym for biologic and often used is literature. **Biogeneric** is a term simply indicates any biopharmaceutical considered generic and used mainly in developing countries that classify the follow-on or non-original products of original biologics. This term was conceived following the chemical generics although it is somewhat wrong because of the difference in nature of chemical and biological drugs. **Follow-on biologic (FOB)** is an approved biopharmaceutical or on track for approval by the FDA as a generic biopharmaceutical. **Biosimilar** is a term that has been extensively used in literature although officially have not been defined for “similar biotechnology medicinal product”. This name actually classifies a new type of generic biopharmaceuticals and associated product’s approval in the European Union and only used to refer products that have already been approved. **Follow-on protein (FOP)** is another homologous term for biosimilar used in the US. These are either approved biopharmaceuticals or on track for approval by the FDA as a generic drug. An exclusive criterion of this category is that it generally refers to simple proteins. Other terms also found infrequently such as ‘similar biotherapeutic products’ or ‘subsequent-entry biologicals’. These terms often creates confusion.
or mislead us to when we see terms like ‘second-generation biologics’ or “biobetters”. Biobetters are truly follow-on biologics that are actually improved version of an original biologic and results from rigorous R&D. Biobetters are developed by originator manufacturer with clinical
advantages over the original biologic (Rader, 2007). However, in order to make a clear image about the terminologies here we present the classification of biological drugs according to IMS health in Figure 1 (Rickwood and Biase, 2013).

![Figure 1. Classification of Different Types of Biological Drugs.](image)

Biologics available nowadays are termed by various different names across the globe. However, here we present a simple classification that IMS Health established and verified by industries. Most of the products fits into this classification and therefore allows consistent analyses across continents, therapy areas and manufacturers.

It has to be frankly understood that within the biotechnology drug industry, definitions are themselves ill-defined and one of the underlying facts is that the products are complex in nature. These complexities create confusion and that is why widely accepted or recognizable definitions are still demanding. For instance, the term generic, similar and follow-on in the context of biopharmaceuticals can have different meanings and connotations. Some people have clear objection about “biogenerics” because it often wrongly gives impressions of inferior quality, links them to generic drug industry and derivative of a less innovative technology. Similarly, to some people “follow-on” implies that they are results of cutting edge technology rather than decades-old “innovator” technology (Rader, 2007). However, throughout this report we will generally annotate all innovator biotechnology drugs as “biologics” and subsequent similar biotech medicinal products generated by another inventor as “biosimilars”.

**WHAT IS A BIOSIMILAR?**

The first ever approved biologic human insulin “Humulin” appeared in 1982 and since then biologics industry has been matured over 30 years. Along with the market their applications has increased and many biologics dominated the market of therapeutics. Inevitably, some of them have already lost their patent protection as well (Table 1). The expiration of patent protection of many biologics has left open the scope for the development of the alternative version of innovator biologics. This non-original version of biologics ate generally known as “Biosimilars”. Not only the patent expiration but also the increasing pressure on healthcare cost created by patented biologics encouraged the rise of biosimilars. Owing to
structural and manufacturing complexities and discrepancies, these non-original biological products are considered as similar, but not generic equivalents of innovator biologics. Therefore, biosimilars can be simply understood as generic substitutes of off-patent innovator biologics (Sekhon and Saluja, 2011; Solanke, 2014).

Precisely, we can define biosimilars as biotechnological medicinal products that are similar in terms of efficacy and safety to an already licensed, well established reference biologics, manufactured by an independent applicant following expiry of patent of that reference product and approved for marketing on the basis of evidence on similarity consolidated by pre-existing scientific and regulatory knowledge. Unlike chemical generics the inherent complexity of biosimilars include several challenges to prove them as same as the originator biologic such as similarity, interchangeability with original biologic, regulation, IPR and public safety. In different market generic versions or similar biological products are termed differently. They are called as “biosimilars” in Europe, “follow-on pharmaceuticals” in the US and Japan, “subsequent entry biologics” in Canada, “biocomparables” in Mexico. However, the important fact is although copied but each biosimilar result from extensive R&D and in that sense they are unique as well. Thus the competition for price cutting biosimilars against original biologics may give rise to second generation of biologics with improved formulation, delivery systems and performance. (Sekhon and Saluja, 2011; Solanke, 2014).

### Table 1 List of Some Patent Expired Originator Biologics

<table>
<thead>
<tr>
<th>Originator Company</th>
<th>Biologic</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genentech</td>
<td>Nutropin (somatropin)</td>
<td>Growth disorders</td>
</tr>
<tr>
<td>Abbott</td>
<td>Abbokinse (eudurase erokinase)</td>
<td>Ischemic events</td>
</tr>
<tr>
<td>Eli Lilly</td>
<td>Humulin (recombinant insulin)</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Genzyme</td>
<td>Ceredase (algglucerase)</td>
<td>Gaucher disease</td>
</tr>
<tr>
<td></td>
<td>Cerezyme (imiglucerase)</td>
<td></td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>Streptase (strepstokinase)</td>
<td>Ischemic events</td>
</tr>
<tr>
<td>Biogen/Roche</td>
<td>Intron A (IFN-α-2b)</td>
<td>Hepatitis B and C</td>
</tr>
<tr>
<td>Serono</td>
<td>Serostim (somatropin)</td>
<td>AIDS wasting</td>
</tr>
<tr>
<td>Eli Lilly</td>
<td>Humatrope (somatropin)</td>
<td>Growth disorders</td>
</tr>
<tr>
<td>Amgen</td>
<td>Epogen, Procrit, Eprex (erythropoetin)</td>
<td>Anemia</td>
</tr>
<tr>
<td>Roche</td>
<td>NeoRecormon (erythropoetin)</td>
<td>Anemia</td>
</tr>
<tr>
<td>Genetech</td>
<td>TNKase (tenecteplase TNK-tPA)</td>
<td>Acute Myocardial Infarction</td>
</tr>
<tr>
<td>Chiron</td>
<td>Proleukin (IL-2)</td>
<td>HIV</td>
</tr>
<tr>
<td>Amgen</td>
<td>Neupogen (filgrastim G-CSF)</td>
<td>Anaemia, Leukemia, Neutropenia</td>
</tr>
</tbody>
</table>

### COMPARISON: CHEMICAL GENERICS vs BIOSIMILARS

This is very much crucial to understand the difference between biosimilars and small molecular drugs or chemical generics. Using specific chemical synthetic methods identical copies of chemical generics can be produced easily (Crommelin et al., 2005). However, identical copies of biologics can hardly be reproduced (Weise et al., 2012). The underlying reasons are size of the protein (100–1000 times larger than a small molecule) and its highly complex three-
dimensional structures. Therefore, the ins and outs of a protein’s functions are often difficult to understand (Kleinberg and Mosdell, 2004; Vital et al., 2013). Moreover, biologics or therapeutic proteins are derivative of highly controlled biological processes that may cause remarkable differences between biosimilar and original biologic although they are identical in protein sequence. Inevitably, it may results in heterogeneities in the structure and function of the resultant molecule (Rathore and Rajan, 2008; Lee et al., 2012). Biologics, such as mAbs and their level of complexities are not only about amino acid sequences rather characterized by their 3-D structure, location of glycosylation sites, isoform profiles and the degree of protein aggregation (Crommelin et al., 2005; Hoglund, 1998; Hooker and James, 1998). Pharmaceutical formulation of the finished biologic is also critically important which may potentially affect 3-D structure of active protein and its aggregation (Kleinberg and Mosdell, 2004; Lee et al., 2012). Pharmacology of biologics i.e. distribution in tissues and binding with its target molecule as well as interaction with other molecules are dependent on these above mentioned properties. Undoubtedly, the structural characteristics of a biologic critically determine its pharmacokinetic (PK) and pharmacodynamic (PD) profile which includes its biological activity, clinical efficacy and safety in therapy (Kleinberg and Mosdell, 2004). A comparison between biologics and small molecular drugs is presented in supplementary Table 1.

MANUFACTURING BIOLOGICS AND CHALLENGES FOR BIOSIMILARS

Biologics encompasses diverse class of biological medicines that are produced and isolated from living systems such as bacteria, yeast and mammalian cells. The manufacturing of a biologic involves several complex steps (Figure 2). First, the target gene sequence is cloned into a suitable expression vector and the putative protein is produced by a suitable cell expression system. These basic steps of expressing a foreign protein in a host expression system are followed by quality control, scaling up, purification and formulation to produce a finished end product. Individual step along the whole process can significantly affect the structure of the target protein (Rathore and Rajan, 2008). Additionally, basic factors such as such as pH, temperature, shearing and the materials of the containers can also impact the quality of the final product (Lee et al., 2012). Among all these, the most critical variable is the expression system for the recombinant protein that determines the 3-D structural features as well as its function. For instance, recombinant human granulocyte colony-stimulating factor (G-CSF) is expressed without any post-translational modification of glycosylation in simpler E. coli host. Same G-CSF results in a glycosylated protein if expressed in a Chinese hamster ovary cell expression system or mammalian host system (Hoglund, 1998). Similarly, difference in post-translational modification level has also been observed in case of with interferon-gamma produced using different expression systems (Hooker and James, 1998). The finished product of chemical generics are generally structurally homogenous (>98%) but biologics can often be a mixture of different isoforms. Moreover, size and complexity of the molecule poses a serious bottleneck to elucidate the optimal isoform proportions in a finished biological product (Kleinberg and Mosdell, 2004). Nevertheless, it is of paramount importance to determine the impure isoforms and their resultant impact on the safety, efficacy and immunogenicity of the finished biologics (Sharma, 2007). The well established phenomenon for biological medicine is that their efficacy hinges on structural properties and their structure leans on methods involved in manufacturing process. Therefore, designing a biologic requires great deal of effort and planning during its R&D phase in order to clinch the quality and integrity of the final product.
COMPARABILITY AND CHANGES TO MANUFACTURING PROCESS

There are cases when a biologic’s manufacturer may bring out changes or alter the manufacturing process. Underlying reasons are enhancement of product quality and yield, adherence with upgraded regulatory policies, increase the efficiency and improving reliability of the manufacturing process (Rathore and Rajan, 2008).

Often routine analytical techniques fail to assess the effect of changes on efficacy and safety. Nevertheless, any changes in process warrants fully fledged non-clinical and clinical evaluations to ascertain its quality. The reality is recombinant biologics have always been treated as a result of complex process and original developers avoided any alteration in the manufacture in order to get rid of regulatory questions. But, the scenario has been developed positively over the years. Nowadays regulatory authorities can easily deal with any sort of analytical characterization owing to their long experiences. This advantage has allowed biologics and biosimilars to be evaluated through a “comparability exercises” for validating a manufacturing process change (Lewis et al., 2010; Putnam et al., 2010). The US Food and Drug Administration (FDA), European Medicines Agency (EMA) and other regulatory bodies developed comparability guidelines through a collaborative effort (FDA (a), (b), 2005; Rathore and Rajan, 2008; EMA (d), (e), 2013). This comparability guideline actually evaluates safety in a primary basis as well as ensures quality. Under this guideline complete risk assessments are carried out analytically. Furthermore, often clinical and nonclinical evaluations are also sought to determine the safety and efficacy (Rathore and Rajan, 2008). In supplementary Table 2, we have presented few examples of changes in manufacturing that ultimately led to clinical studies for re-evaluation of the resultant impact on manufacturing process as well as safety and efficacy of the product.

Figure 2. Steps Involved in Manufacturing of a Biologic Product. Manufacturing a biologic involves a number of steps and starts from cloning the target gene in a vector and its subsequent expression in a suitable host. Level of complexity arises in further steps as well as with the scaling up of the manufacturing processes (Adapted from Sekhon and Saluja, 2011).
“Pharmacovigilance” is the term that is intricately related with biosimilars development and particularly with the approval process. For each biosimilar medicinal product it should be taken into account and emphasized that number of patients studied prior to registration process. Particularly, for a developing country this is more important. This is also critical in case of transboundary movement of biosimilar products. Pharmacovigilance is nothing but a risk assessment and management programme that always compares biosimilars with reference biologic product. Well established patient registries across the world are wealthy resources and collaboration with them will be critical in developing these capacities. Generally a pharmacovigilance programme for a under developed biosimilar deals with adverse effects, novel safety signs and measurements, accurate immunogenicity information for individual patient and traceability of the drug associated with an event (Müller, 2014).

BIOSIMILARS AND THE KNOWLEDGE GAP
Whenever a company starts developing a biosimilar generally they begin with a knowledge gap. Although the original biologic may go off patent but the manufacturing processes are by and large proprietary and thus not publicly accessible. Once the target product is identified for a biosimilar, a manufacturer usually work in an opposite direction to develop the whole process including protein expression system, scale-up, purification, formulation and packaging. All these steps have to be capable of reproducing the similar biologic or follow-on product so that similar analytical, clinical and preclinical characteristics can be achieved. In fact they are essential for the approval process. EMA in the EU approves a biosimilar only after they are satisfied with clinical study in comparison to original biologic. They have developed this regulatory policy taking the knowledge gap in account. In spite of these stringent requirements, there are instance of biosimilar approval in the EU with altered physiochemical and immunogenicity profile compared to original biologic products (Miletich et al., 2011). For example, a filgrastim biosimilar showed differences in exposure and an epoetin biosimilar showed differences in titrated dosing (Schellekens and Moors, 2010). Interestingly, regulatory authorities ruled out these differences in case of these two biosimilars assuming that these would unlikely to affect the safety or efficacy of the products. However, bizarre and unexpected clinical findings indicate that biosimilars cannot be the exact copy of originators and structurally related molecule can exert functional differences. Thus, detailed clinical investigation is the critical step in biosimilar development (Miletich et al., 2011).

BIOSIMILARS AND REGULATORY REQUIREMENTS
It has been couple years since FDA (FDA(c), (d), (e), 2012), The EMA (EMA (a), 2005; EMA (b), 2006; EMA (d) 2013) and Swissmedic (Swiss Regulatory Agency) (Swissmedic (a), (b), 2014) have outlined the guidance for approval of biosimilars. The EMA has already dealt with small size biosimilars (insulin, interferon, filgrastim, epoetin and somatropin) (Rathore and Rajan, 2008). During 2006–2011 time periods, a number of biosimilars went through EMA regulatory review pipeline. Six of those biosimilars demonstrated aberrant results that were not foreseen during nonclinical testing. Out of six, four were rejected because of their compromised efficacy and safety compared to the originator products. Among two other manufacturers, one altered the manufacturing process and another was withdrawn prior to marketing authorisation (Rathore and Rajan, 2008).

To regulate more sophisticated mAb based biologics, the EMA published a “Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical
issues” back in 2012 (EMA (c), 2012). Under this guideline, each biosimilar mAb will have to show in vitro and in vivo results in nonclinical phase. Inevitably, detailed bioequivalence (BE) profile will have to be presented emphasizing a similar clinical PK profile compared to originator mAb. Because of the high variability of PK in case of mAbs, this particular parameter is regarded as an essential component for evaluating efficacy. Similarly, PD studies are also important for appraising comparability which ultimately gives a measure for safety. The Swissmedic regulatory policy for biosimilars approval is predominantly based on the EMA guidelines. But, this guideline stringently recommends clinical trial to be conducted on “most sensitive” and homogenous patient population for evaluation purpose (EMA (c), 2012; Mellstedt, 2013; Swissmedic (a), 2014). We have shown some currently approved biosimilars worldwide in Table 2.

### Table 2 Currently Approved Biosimilars Worldwide

<table>
<thead>
<tr>
<th>Biosimilar</th>
<th>Brand</th>
<th>Manufacturer</th>
<th>Approval Year</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoetin alfa</td>
<td>Abseamed</td>
<td>Medice</td>
<td>2007</td>
<td>EU</td>
</tr>
<tr>
<td></td>
<td>Binocrit</td>
<td>Sandoz</td>
<td>2007</td>
<td>EU</td>
</tr>
<tr>
<td></td>
<td>Epoetin alfa hexal</td>
<td>Hexal</td>
<td>2007</td>
<td>EU</td>
</tr>
<tr>
<td>Epoetin zeta</td>
<td>Retacrit</td>
<td>Hospira</td>
<td>2007</td>
<td>EU</td>
</tr>
<tr>
<td></td>
<td>Silapo</td>
<td>Stada</td>
<td>2007</td>
<td>EU, Serbia</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Biograstim</td>
<td>CT Arzneimittel</td>
<td>2008</td>
<td>EU</td>
</tr>
<tr>
<td></td>
<td>Filgrastim hexal</td>
<td>Hexal</td>
<td>2009</td>
<td>EU</td>
</tr>
<tr>
<td></td>
<td>Filgrastim Ratiopharm</td>
<td>Ratiopharm</td>
<td>2008</td>
<td>EU</td>
</tr>
<tr>
<td></td>
<td>Nivestim</td>
<td>Hospira</td>
<td>2010</td>
<td>EU, Australia</td>
</tr>
<tr>
<td></td>
<td>Ratiograstim</td>
<td>Ratiopharm</td>
<td>2008</td>
<td>EU</td>
</tr>
<tr>
<td></td>
<td>(Withdrawn in 2012)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TevaGrastim/Grasalva</td>
<td>Teva Generics</td>
<td>2008</td>
<td>EU, Lithuania, Russia</td>
</tr>
<tr>
<td>Somatropin</td>
<td>Omnitrope</td>
<td>Sandoz</td>
<td>2006</td>
<td>EU, US, Canada, Australia, Japan</td>
</tr>
<tr>
<td></td>
<td>Valtropin</td>
<td>BioPartners</td>
<td>2006</td>
<td>EU</td>
</tr>
<tr>
<td></td>
<td>(Withdrawn in 2012)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infliximab</td>
<td>Inflectra</td>
<td>Hospira</td>
<td>2013</td>
<td>EU</td>
</tr>
<tr>
<td></td>
<td>Remsima</td>
<td>Celltrion</td>
<td>2013</td>
<td>EU</td>
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### GLOBAL MARKET LANDSCAPE OF BIOLOGICS AND BIOSIMILARS

Since the inception, biologics have become celebrities in pharmaceutical industry. They have shown amazing acceptance over past 30 years with sales growth as twice of the overall market. At the moment, six out of top ten pharmaceuticals are biologics. According to IMS health, the global biologics market size reached nearly $170 billion by 2012, which was 18% of the pharmaceutical market value. As shown in Figure 3, the US has the lion’s share (49%) of the global biologics market value. Expectedly, the US alone also provided almost half of the sales growth of biologics. On the other hand, the EU occupies 22% of the market share and 14% of growth. The emerging markets in rest of the world show a sharp contrast against two large markets and stands with...
a 7.5% share. Apparently, it is visible that biologics market value and growth are still confined in mature markets. This phenomenon is strikingly different in pharmaceutical market where “phar merging” markets of developing countries have largely kept up the growth (Rickwood and Biase, 2013).

Figure 3. Global Market Trends of Biologics. Over a period of seven years global biologics sales has been growing although market growth has not been uniform. In terms of sales and growth, US possess the largest market followed by EU. Due to advent of biosimilars, total biologics market growth in phar merging countries is increasing. (Source: IMS Health; Rickwood and Biase, 2013)

Biologics innovators exploited the performance to its full but has put tremendous pressure on healthcare budgets worldwide. The obvious reason is that biologics are costly pharmacotherapies. What great this pressure has done is opened the opportunities for less expensive alternatives or biosimilars per se for “off-patent” biologics (Table 1). The global landscape of biosimilars and non-original biologics market is rapidly changing. Since the biosimilar regulatory pathway enacted in the EU in 2005, three biosimilars against three original biologics were approved. These are somatropin (to treat growth failure), erythropoietin (to treat anaemia) and filgrastim (to boost white blood cell counts after chemotherapy). From that point until 2013, no new biosimilars entered in EU market or in the US for lack of a biosimilar approval pathway. This period was relatively calm because of the slow uptake of biosimilars. After 2013 the situation has been changing dramatically that some indications has reflected. 1. The first mAb biosimilars has been approved. 2. A non-original version of filgrastim that was in the EU market has been approved for marketing in the US. For the first time, it is apparently becoming clear that a biosimilar has eclipsed an originator product. 3. EMA permitted a biosimilar manufactured outside EU (by a Korean manufacturer). 4. Some large biologic therapeutic areas are on the verge of facing loss of exclusivity (LoE) in the next few years including mAb oncologics, modern insulins and anti-tumor necrosis factor mAbs (anti-TNF mAbs).
Considering these indications it has been speculated that biosimilar market in coming decade will show an upward trend and will bring out a paradigm shift in the business. In this changing scenario, Multi-National Corporations (MNCs) largely focused their efforts on mature markets and in parallel local contenders are emerging in the regional and international market by building their capacity.

**THE GLOBAL FORECAST**

The global market landscape of biosimilars is not uniform rather disparate. In developed countries such as in Japan, Canada and the EU the biosimilars only have taken 5% market of originator biologics. In contrast, emerging nations i.e. China, Brazil, India, Korea and Mexico allowed biosimilars to occupy 20–60% of the total cost of biologicals. The obvious reason is that regulatory approval of biosimilars in the developing world is much easier than developed world. Nevertheless, it is expected that once blockbusters start go off-patent in the EU, biosimilars will be 20–30% cheaper than biologics. Market competition will play a pivotal role in favour of biosimilars. These speculations resultant form the fact that 30–40% price reduction has already been seen for originator epoetin and filgrastim (Mellstedt, 2013).

The sole purpose of biosimilars development is lowering the cost of original biologics and takes their market share. IMS Health forecasts that the global biologics market is expected to reach $200 billion by 2016-2017 and $250 billion by 2020. Currently biosimilars occupied only 1% of it (Blackstone, 2012). Up to 2020, some blockbusters mAbs such as infliximab, adalimumab, rituximab, cetuximab, trastuzumab and bevacizumab will continue to dominate because of patent protection. Once biosimilar mAbs will start invading the market the scenario will change dramatically. Biosimilars and non-original biologics is likely to take 4-10% by 2020 which will worth $10 – 25 billion. This anticipation hinges on the number of biosimilars and most importantly on the number of biosimilars introduced in the US market (Figure 4). The underlying fact is, the US harbours largest market of biologics due to highest per capita consumption of biologics. By 2020, the biologics sector will go through its own patent cliff. Twelve biologics that shares 40% of the global biologic market at present and are worth $72 billion in sales will face patent expiration. These 12 compounds include blockbuster biotech drugs such as Humira®, Enbrel®, Remicade® and Lantus® (Figure 5). This is no way difficult to imagine that this goldmine will be too lucrative for biosimilars to be kept aloof. In fact, the race has begun already. In September 2013, EMA approved first two biosimilars for Remicade as Inflectra™/Remsima™. By now, these two biosimilars only incur more sales than rest of the biosimilars in the market (Rickwood and Biase, 2013).

**BIOSIMILARS: OPPORTUNITIES FOR PHARMERGING COUNTRIES**

Biosimilars are not easy to develop compared to small-molecule generics. It requires high investment, technical capability and clinical trial facilities as well as assessment expertise. Manufacturing biosimilars involves sophisticated technologies and scaling up could be an issue. On an average, a biosimilar development may cost $40-$300 million, whereas a chemical generic may incur only $1-4 million. This exemplifies that fact that with these huge investments, technical and operational management system will have to be developed. In terms of regulatory process developed markets are more complex than underdeveloped or developing markets. But, currently biosimilars compete less on price than chemical generics. Generally a biosimilar price is around 20-30% lower than original biologic, which could be 70-80% lower in case of chemical generics compared to originator brand.
Figure 4. Global Market Forecast for Biologics and Biosimilars. This figure shows the trend in global biologics market. Biosimilars are gaining their market gradually. It is now expected that biosimilars will take 4-10% market share of $250 billion biologics market worldwide by 2020. CAGR (Compound annual growth rate) of biologics (9%) between 2007-2012 was much lower than biosimilars (34%). Therefore, in 2012 original biologics took 1.4% market share which was only 0.5% in 2007. By 2020, biosimilars will grow another 21-34% and likely to be a market of $11-25 billion (Source: IMS Health; Rickwood and Biase, 2013).

Figure 5. Patent Expiry Timeline for Top Biologics. In next five years most of the blockbuster biologics will go off-patent. These enlisted twelve biologics only earn $72 billion that equals to 40% of the global biologics market. The patent cliff of these biologics will inevitably cause invasion of biosimilars in the market. Already EMA approved two biosimilars for infliximab were approved as Inflectra™/Remsima™ in September 2013. (Source: IMS Health; Rickwood and Biase, 2013).
Moreover, a large amount of money has to be invested for creating market as there is no automatic market exists for biosimilars as well as developing awareness among physicians about the safety and efficacy. Taking these all together biosimilar development needs long term business strategies that may potentially discourage small pharmaceutical enterprises (Rickwood and Biase, 2013).

The size of global biosimilars and non-original biologics market was $2.4 billion in 2012, which is a small part of the biologics market but the positive sign is that it has been growing. The market is growing slowly in Europe with more nations embracing the concepts under EMA guidelines. Following, the “gold standard” of EU the US, Canada, Japan and South Korea established very stringent and clear biosimilars approval pathway. Among BRIC’s countries India, China, Brazil and Russia also set approval pathways. These guidelines are all diverse but it can be accepted that in near future a global and uniform standard will develop by accommodating all of them. All that it means these nations have already opened the door for biosimilars. The truth is the impact of biosimilars and non-original biologics are quite significant in developing countries. Some developing economies such as India and China have aggressively taken the advantage of biosimilars to surpass originals. Market of non-original biologics and biosimilars are by and large distributed in Brazil, Russia, India, and China (BRIC) which account for nearly all (91%) of the market value among 16 pharmerging markets. Although there are differences in biosimilar demand and usage but in general Russia and Brazil have fewer players and higher prices and China and India have many players and lower prices biologics (Rickwood and Biase, 2013).

Some large MNCs and even some governments are investing heavily in biosimilar development. Current market players are mainly global R&D-based pharmaceutical and biotech companies dominating mature markets. On the other hand, some generics manufacturers and local biosimilar manufacturers also entered in emerging markets. It is apparently clear that the number of players will increase and intensify the competition very soon. This speculation is evident from Figure 6. Large pharmaceuticals have lost market share to emerging local players in pharmerging markets. In tenure of ten years (2003-2013), they have lost 15% of their business in emerging markets. This has been followed by the biologics as well. Local players have gained biologics and recombinant therapeutics market by 5% and 3% respectively. Therefore, it is evident pharmaceutical giants are giving-up shares to small and medium sized companies. If this trend goes on, then large pharmaceuticals are expected to lose additional 7-8% market share by 2023 that will leave several billion dollars for emerging market player (Rickwood and Biase, 2013). Interesting fact is that, emerging market players are segmented. A portion of them strictly domestic companies (Sotex, Hayao, Demi Ilac, SG Bio), some are regional market players (Dr. Reddy's, Shanghai CP Guojian, Bioton, Kalbe Pharma) and quite a few of them are actually international players (Sandoz, Teva, and Celltrion). Among the domestic players, 9 out of the 10 Chinese companies only serving their own market whereas Indian companies are looking at domestic market in East Asia. Some of the Latin American companies have gone beyond continental territory and one of them has occupied the largest biosimilar player in Russia. Some of the domestic companies have engaged government and working with their funding. Two exclusive examples are PharmADN in Argentina and Bionovis in Brazil. Perhaps, the most ambitious government in this world is in South Korea who aims to boost local companies to capture 22% of the global biosimilar market by 202. It will not be any strange if we see electronic giant “Samsung” in biosimilar industry in near future (Rickwood and Biase, 2013).
Figure 6. Growth of Local Players in Emerging Markets. This figure illustrates a significant trend in global biosimilar market. Due to growth of local companies, large pharmaceuticals or MNCs are losing their dominance in emerging markets. Over a ten years period of 2003-2013, large pharmaceuticals have lost 8% of their share of biologics to pharmerging players. If this growth continues, then in next decade (2013-2023) pharmerging players will gain another 7-8% and most of it will be possessed by biosimilars. Therefore, it indicates that local companies will be taking over the biosimilar market gradually. (Source: IMS Health; Rickwood and Biase, 2013)

In some pharmerging markets governments are supporting the growth of biosimilar industry in many different ways. By backing the manufacturers with pro-local regulations they are trying to embark on a platform for the development of biosimilars and biologics in future. Pragmatic vision and investments by the governments in China, Russia, South Korea and Brazil will give return in a decade from now. The South Korean government is stimulating biosimilar industry growth with financial incentives, tax breaks and support in creating biotechnology clusters. The Chinese government has adopted the strategy to offer incentives in order to encourage local players to partner with MNCs and subsequent technology transfer. Russia has prioritized local biosimilar industry growth and set their clear goal to produce 57 enlisted drugs locally. Under the guidance of national policies Brazil set out to develop the biotech capacity and industry. As part of this endeavour, “Productive Development Partnerships” (PDPs) between government institutions and private laboratories are emphasized. PDP aims to build-up capacities of public and local producers to manufacture strategic
products including biosimilars. Up to date, 63 PDP have been signed and most of them focused therapeutics that will eventually take on the challenges of biosimilar development. From these monumental examples it is understood that taking the market of biosimilar requires capacity building of both public and private entities (Rickwood and Biase, 2013). Not only are the developing countries, some pharmaceutical companies from LDCs are also aspiring to be biosimilar suppliers. LDCs that have strength in pharmaceuticals (e.g. Bangladesh ranked top among 49 LDCs in pharmaceutical sector) must come forward and learn the lessons from forerunners to take the opportunities of this growing market.

CONCLUSION

From this report is should be understood that demand for biologics is increasing as healthcare sectors are more inclining towards them compared to small molecular drugs. Because of their high prices cost-effectiveness has been sought for treating diseases through biosimilars for off-patent biologics both in developed and developing countries. We have seen innovators and emerging suppliers adopted some strategies to develop their capabilities to compete in the biosimilar market. Along with investments in manufacturing and analytical methods, regulatory processes are also deemed challenging which may change the course of the business in future. Another significant facet of the rise of biosimilars is that cheap production capabilities in developing countries can potentially disrupt current market dynamics and patient care around the world. However, from scientific point of view the quality of pharmacodynamic (PD) assays utilized, comparability in pharmacokinetics (PK), immunogenicity and quality of clinical data will be critical for biosimilars to gain a market. Moreover, to remain in the market pharmacovigilance will be essential to demonstrate safety and efficacy in long run. In addition consistent production of biosimilars for a long-term is yet to prove. Even after all these challenges, biosimilars are bringing out several opportunities for emerging economies. An expected wave of biosimilars is incumbent but perhaps at this stage it is not easy to imagine the course of this business. Large MNCs, local and regional companies, regulatory agencies and health authorities have their own distinguished role to take the advantage of it. They must also act in concert to allow biosimilar accessibility in a safer way to people around the world.

REFERENCES


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Supplementary Table 1. Comparison of Small Molecular Drugs and Biologics (Sekhon and Saluja, 2011)

<table>
<thead>
<tr>
<th></th>
<th>Small Molecular Drugs</th>
<th>Biologics</th>
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<tbody>
<tr>
<td><strong>Product</strong></td>
<td>Produced by chemical synthesis</td>
<td>Biotechnologically produced by host cell lines</td>
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<tr>
<td>Low molecular weight</td>
<td></td>
<td>High molecular weight</td>
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<tr>
<td>Well-defined physiochemical properties</td>
<td></td>
<td>Complex physiochemical properties</td>
</tr>
<tr>
<td>Stable</td>
<td></td>
<td>Sensitive to heat and shear (aggregation)</td>
</tr>
<tr>
<td>Simpler 3D structure</td>
<td></td>
<td>Complex 3D structure</td>
</tr>
<tr>
<td>Single entity, high chemical purity, purity standards well established</td>
<td></td>
<td>Heterogeneous mixture, broad specification which may change during development, difficult to standardize</td>
</tr>
<tr>
<td>Administered through different routes of administration</td>
<td></td>
<td>Usually administered parenterally</td>
</tr>
<tr>
<td>Rapidly enters systemic circulation through blood capillaries</td>
<td></td>
<td>Larger molecule primarily reach circulation via lymphatic system, subject to proteolysis during interstitial and lymphatic transit</td>
</tr>
<tr>
<td>Distribution to any combination of organ/tissue</td>
<td></td>
<td>Distribution usually limited to plasma and/or extracellular fluid</td>
</tr>
<tr>
<td>Often specific toxicity</td>
<td></td>
<td>Mostly receptor mediated toxicity</td>
</tr>
<tr>
<td>Often non-antigenic</td>
<td></td>
<td>Usually antigenic</td>
</tr>
<tr>
<td><strong>Manufacturing</strong></td>
<td>Completely characterized by analytical methods</td>
<td>Difficult to characterize</td>
</tr>
<tr>
<td>Easy to purify</td>
<td></td>
<td>Lengthy and complex purification process</td>
</tr>
<tr>
<td>Contamination can be generally avoided, is easily detectable and removable</td>
<td></td>
<td>High possibility of contamination, detection is harder and removal is often impossible</td>
</tr>
<tr>
<td>Not affected by slight changes in production process and environment</td>
<td></td>
<td>Highly susceptible to slight changes in production process and environment</td>
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Clinical Development

- Often only Phase I studies
- Extensive clinical studies, including Phase I–III
- Short timeline for approval
- Pharmacovigilance and periodic safety updates needed

Regulation

- Needs to show bioequivalence
- Needs to demonstrate comparability and similarity
- Abbreviated registration procedures in Europe and US
- Regulatory pathway defined by EMA (EU), FDA (USA), Swissmedic (Switzerland)
- Automatic substitution allowed
- Currently no automatic substitution
- Intended or allowed

Cost

- Lower ($1-4 million)
- Higher ($10-400 million)

Supplementary Table 2. The Consequences of Altered Manufacturing Process for Registered Biologics (Adapted from Müller, 2014)

<table>
<thead>
<tr>
<th>Product</th>
<th>Process Change</th>
<th>Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avonex® (interferon beta-1a)</td>
<td>New cell bank used</td>
<td>This change in the manufacturing process was not pursued, due to unexpected clinical outcomes</td>
</tr>
<tr>
<td>Raptiva® (efalizumab)</td>
<td>Manufacturing transferred to a new organization</td>
<td>Additional clinical studies needed</td>
</tr>
<tr>
<td>Myozyme® (alglucosidase alfa)</td>
<td>Manufacturing process scale-up within the same organisation.</td>
<td>Additional clinical studies needed.</td>
</tr>
</tbody>
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