BIOSIMILARS: GLOBAL SCENARIO AND CHALLENGES

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ABSTRACT

Biologics are a major growth driver for global pharmaceutical market. Biosimilars are those biologics which are developed after patent expiration of innovator biopharmaceuticals. They are known as similar biologics, follow-on biologics, follow-on protein products, subsequent-entry biologics, bio-comparables, second-entry or off-patent biotechnology or multisource products in different countries. They require separate marketing approval since they are not generic versions of biologics. They are rather new molecules owing to a number of heterogeneities as compared to the reference innovator biologics. Hence, they require full documentation on quality, safety and efficacy. Several challenges in the form of structural variability, immunogenicity, regulatory, etc. impede the way of growth of biosimilars. Structural variability results due to the complexity of structure of biologics. Immunogenicity is inherent to these products since they are proteins. The lack of a robust regulatory framework poses a risk to patient safety. This article aims to highlight the biosimilars scenario on a global basis and it throws light on the regulatory guidelines of different countries. It also discusses the major challenges involved therewith. It also considers some trends that promise the bright future of biosimilars.

Key words: Biosimilars, Biologics, Quality, Safety, Efficacy, Structural Variability, Immunogenicity, Regulatory.

INTRODUCTION

Biologics or biopharmaceuticals or bio technologically produced drugs are a major growth driver for the global pharmaceutical market. These are medicinal products which contain proteins derived from DNA technology and hybridoma techniques. Living organisms such as plant and animal cells, bacteria, viruses and yeasts are used for the production of biologics (Misra M, 2012). Biologics are copies of endogenous human proteins that are characterized by complex three-dimensional. These are high molecular weight compounds and are unique as they are manufactured by using living cells. These extend human abilities to fight diseases and are useful to mitigate even incurable orphan diseases. Most biologics replace or supplement a natural protein produced by the body. Hence they satisfy medical needs that were previously unmet by chemical drugs. The class of biologics is rapidly growing and includes biological factors such as cytokines, hormones, clotting factors, monoclonal antibodies, vaccines and molecules used for cell/tissue-based therapies. These drugs are far more complex with regard to their structure and mode of action than traditional chemical drugs. The prediction and exploration of the exact mode of action of biologics is extremely difficult due to their complexity. For example, recombinant interferon interacts with nearly 100 genes. This poses many complex questions related to its study (Nowicki, 2007). Biosimilars are those biologics which
are developed after patent expiration of innovator biologics. They require submission of separate marketing approval. Hence, it can be said that biosimilars (European Medicines Agency, EMEA) or follow-on biologics (Food & Drug Administration, FDA) have emerged as a third market dynamic between original products and generics.

A generic may be defined as a drug containing the same active ingredients and showing equivalence as the original small-molecule pharmaceutical that has been produced using chemical synthesis. A biologic is a complex biopharmaceutical, produced using r-DNA technology, controlled gene expression or antibody technologies like hybridoma technology (Bruckner M et al., 2009; Misra, M, 2012). Its examples include biological proteins (cytokines, hormones and clotting factors), monoclonal antibodies, and vaccines (Misra M, 2012). A Biosimilar is an approved drug that has been produced by using biotechnology. An innovator biologic is used as a reference (Bruckner M et al., 2009).

Biosimilars are known as similar biologics, follow-on biologics, follow-on protein products, subsequent-entry biologics (Canada), biocomparables (Mexico), second-entry, and off-patent biotechnology or multisource products in different countries (Schellekens H, 2004; Sekhon BS, 2011; Undela K, 2012). They are intended to have the same mode of action for the same diseases as the innovator biologics (Undela K, 2012). Biosimilars cannot be considered as “biological generics” due to their structural and manufacturing complexities. It should be noted that it is not possible to duplicate the innovator biologic’s production process (Roger SD, 2006). Biosimilars are unique molecules and often only limited clinical data is available at the time of approval. Hence, there are concerns about their safety and efficacy of (Nowicki M, 2007) and extensive data collection studies must be done. The amount of data that is required for the market approval of biosimilars is more than that for a typical generic drug application but it is lesser than for a new biologic application. They cannot be considered interchangeable with the reference innovator biologic. (Schellekens H, 2009).

The Evolution of Biosimilars

A new generation of chemotherapeutical agents, biologics, was born in mid-nineties. The generic versions of innovator biologics appeared in pharmacies on their patent expiry (Gascon P, 2012). Biosimilars are “similar but not the same” or in other words biosimilars are “the twin but not the clone” to the reference innovator biologic (Sekhon BS et al., 2011).

In 2007, the biologics market grew noticeably fast with a double-digit growth of 20%. They generated $95 billion of sales which amounted to approximately 15% of global Pharma revenues (Blackstone et al., 2012). Many approved biologics have already become enormous blockbusters like Enbrel (Amgen/Wyeth), Remicade (Centocor/J&J) and Rituxan (Biogen Idec / Genentech/Roche). Also, the pipelines of the pharmaceutical industry are filled with more than 500 biologics which are in various stages of development. The global biosimilars market is expected to be worth $19.4 billion by 2014, growing at a Compound Annual Growth Rate (CAGR) of 89.1% from 2009 to 2014 (Cai XY et al., 2013).

Development Stages of Biosimilars

There are four stages in the development of a biosimilar:
1) Product development and comparative analysis;
2) Process development, scale up and validation;
3) Clinical trials;
4) Regulatory (EMEA, WHO and FDA) review and approval.

All stages come with varying requirements and take varying amounts of time contributing to the overall cost of developing a biosimilar. The timeline for the development of biosimilars extends up to 8 years (Figure 1) (Brown C et al., 2009) and includes host cell copying, making cell-banks, process development, scale-up and comparability testing.

What encourages biosimilar market growth?

Biologics have dramatically altered the management of uremic anemia. The introduction of erythropoietic agents, prevention and treatment of transplant organ rejection and the use of monoclonal antibodies have given an impetus to the growth of biologics (Roger SD, 2006). The ever-increasing cost of pharmaceuticals asks for reduction of fiscal cost of these interventions so as to increase patient access and to limit the rapidly expanding health-care budget. The arrival of generic versions of chemical drugs as well as biosimilars and attempts made by regulatory authorities to cap costs has come as a relief. Biosimilars have already gained entry in the fields of nephrology, oncology, and hematology.

WHO guidelines

As part of its “Biological Standardization Process” the World Health Organization has developed a framework of general principles. These seek to govern the scientific aspects of biosimilars approval. WHO defines a biosimilar as a “biotherapeutic product claimed to be ‘similar’ in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product (RBP) which must have been licensed by national regulatory authorities on the basis of a full registration dossier” (Undela K, 2012). It labels a biosimilar as a “similar biological product” (SBP). The WHO recommends that the SBP should be clearly identifiable by a unique brand name. It also states that the International Nonproprietary Name, INN must also be mentioned (Niederwieser D et al., 2011). However, WHO
emphasizes that its framework is generalized and it will only apply to well-established biologics on market. It seeks to rationalize clinical requirements majorly and states that at least one clinical study will be necessary for a biosimilar to be approved. Its prime concern is the matter of immunogenicity. The WHO also requires the applicants to include a plan for post-marketing safety assessments in the application made for marketing approval. However, some important debates like interchangeability or substitution and intellectual property are unaddressed by WHO since these are not within its mandate as an advisory body (Brown C et al., 2009).

**Biosimilars: Global Scenario**

**Europe**

The first major player to develop a regulatory model for biosimilars is the European Union. A legal basis for evaluation and approval of similar biologics in Europe was established with Directive 2001/83/EC of 6 November 2001, as amended by Directive 2003/63/EC of 25 June 2003, which entered into force on 1 July 2003 (called Annex I). Further developments were brought with the ‘Pharmaceutical Legislation Review’, in particular Directive 2004/27/EC of 31 March 2004 that amended Directive 2001/83/EC, to authorize the abbreviated approval of biologics that claim to be similar to an innovator product. This entered into force on 30 October 2005 (Roger SD, 2006). However, the legislation left a wide margin of discretion to the Committee for Medicinal Products for Human Use (CHMP) of the EMEA to develop product class-specific guidelines that would determine the extent of non-clinical and clinical tests required (Som N, 2010). Hence in 2005, the EMEA/CHMP issued an overarching biosimilars guideline along with two guidelines for consultation on the quality, non-clinical and clinical issues and immunogenicity to be considered for the development of biosimilars (Nowicki M, 2007; Roger SD, 2006; Schellekens H, 2009). Since 2006, EMEA has been improvising and releasing guidelines covering several different types of recombinant proteins, including insulin, granulocyte-colony stimulating factor (G-CSF), somotropin and erythropoietin, as well as low-molecular weight heparins (Chu R et al., 2009).

There are several biosimilar G-CSFs approved in Europe: Biogranstim®/Filgrastim ratiopharm/Ratiograstim®/ Tevagrastim ® (XM02); Zarzio® and Nivestim® etc (Table 1) (Gascon P, 2012).

The first generation of biosimilars was launched using the abbreviated pathway for similar biologics established by EMEA. This marked the “Biosimilars 1.0” period. Over the next several years improving regulations, analysis, process development and manufacturing capabilities and a global market spanning the International Conference on Harmonization regions, as well as the emerging markets will mark the beginning of the second era of biosimilars (“Biosimilars 2.0”). The Biosimilar 1.0 period was characterized by the definition of the initial framework. On the other hand, the Biosimilar 2.0 period will be marked by challenges in the manufacturing and clinical development of complex products, global harmonization of standards and the increasing demand for long-term safety and efficacy data (Miletich J et al., 2011).

**United States**

The Drug Price Competition and Patent Term Restoration Act better known as Hatch–Waxman Act of 1984 (Nellore R, 2010), designed to deal with generic chemical drugs, was not intended to account for biosimilar versions of biologics (Roger SD, 2006). A biosimilar approval pathway was established by the Biologics Price Competition and Innovation Act of 2009. It was signed into law as part of the Patient Protection and Affordable Care Act of 2010 (Niederwieser D et al., 2011). On February 9, 2012, FDA issued three draft guidance documents intended to facilitate the submission of marketing applications for biosimilars (Mahinka SP et al., 2012):

- “Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009” (Biosimilars Q&A)
- “Scientific Considerations in Demonstrating Biosimilarity to a Reference Product” (Biosimilars Scientific Guidance)
- “Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product” (Biosimilars Quality Guidance)

The FDA follows ‘totality-of-the-evidence’ approach and reviews detailed information including complete analytical testing, clinical immunogenicity evaluation, animal studies and human clinical trials.

The American market, including North America and Latin America, is expected to account for nearly 35.3% of the total revenues in 2014. Biologics worth $25 billion are going to be off patent by 2016 and this will open a pathway for the drug manufacturers to increase their market share, profit margins and reduce the medical expenditure of biosimilars (Pise S et al., 2011). Epogen®, Procrit®, Eprex®, Aranesp® are the biosimilars currently available in the United States (Schellekens H, 2009).

**Canada**

Omitrope was the first biosimilar of Canada. It was approved even before the regulations were finalized. Canada’s approach in terms of safety reflects that of EMEA, but it takes a step ahead and addresses intellectual property debates. Canada’s biosimilar framework is flexible in the biosimilar applicant’s choice of which innovator biologic it uses as its reference;
 unlike the other major frameworks, the innovator biologic may be one that has not been approved and marketed in Canada. This approach serves to encourage biosimilar applicants. However, Health Canada (Canada’s department of health) recommends utilizing those innovator biologics that have been approved by jurisdictions with which it has “an established relationship” (Brown C et al., 2009).

China

China offers several advantages in biologics manufacturing including a highly skilled workforce and relatively well-established infrastructure and technology systems. Biosimilars produced in China include products such as the interferon series, erythropoietin, colony-stimulating factor series, tumor necrosis factor, insulin, growth hormone, and interleukin-2. Most biosimilars have been developed in Western countries such as the United States but China has come to the forefront due to increase in its R&D capabilities (Minevich M et al., 2005).

Japan


Australia

In June 2006, the Therapeutics Goods Administration adopted the European guidelines for registration and approval of biosimilars (Niederwieser D et al., 2011).

The Indian Front

The pre-1995 product patents do not apply in India due to the Trade-Related aspects of Intellectual Property Rights (TRIPS) agreement. This meant that as many as 48 biologics that were patented prior to 1995 were marketable in India (Som N, 2010). Moreover, the innovators had not sought patent protection for some drugs in India, thereby creating a strong opportunity for Indian companies to influence the huge domestic market. This led to the Indian supply of biosimilars to other countries where these products are not patented (Nellore R, 2010). Furthermore, the expiry of the patents of first generation biologics like EPO, G-CSF, human growth hormone, insulin and interferon gave companies the opportunity to enter a new, attractive market.

In India, Phase I-II trials are typically not generally required for biosimilar approval. These may be carried out in special cases. The establishment of bioequivalence requires Phase III trials with a minimum of 100 patients. Therefore, the total cost to develop a biosimilar in India ranges from $10 – 20 million. This helps Indian companies to offer their products at a 25-40% cheaper price than the innovator biologics. Also, normally all biotechnological products are free from Indian government price control except Insulin (Desai JP, 2009).

At present, India is one of the leading contributors in the world biosimilar market. India has demonstrated the greatest acceptance of biosimilars, which is reflected from over 50 biopharmaceutical brands getting marketing approval (Langer E, 2008). The Indian biotechnology industry had revenues of over U.S. $2 billion in 2006, 70% of which was biologics. Companies like Biocon, Dr. Reddy’s Lab., Wockhardt, Cipla Pharmaceuticals have already tapped the biosimilar product opportunity (Mody R et al., 2008). Biosimilars have paved their way in India due to the regulatory authorities (Table 2) and regulatory guidelines coming into force (Table 3) (Malhotra H, 2011).

[GLP - Good Laboratory Practices; DCGI - Drug Controller General of India; CT - Clinical Trial; GMP - Good Manufacturing Practices; DSMD - Data Safety & Monitoring Board; CTD - Clinical Trials Dossier; PMS – Post Marketing Surveillance; PV - Pharmacovigilance; PSUR - Periodic Safety Update Report]

The Indian Pharmacopoeia 2007 contains monographs for ‘r-DNA Biotechnology Products of Therapeutic Value’ including Erythropoietin Concentrated Solution, Granulocyte Colony Stimulating Factor, Human (Filgrastim), Interferon alfa-2 concentrated solution, Streptokinase. The general monograph states, “The product being a protein may cause immunological sensitization in the recipients and therefore needs a high degree of characterization. Testing of the product for safety, identity, strength, quality and purity are similar to those applied to other pharmaceutical products, although the tests themselves may require some modification due to the pretentious nature of the active compound.” “r-DNA derived products suffer from a danger of micro-heterogeneity in the expressed protein and therefore require extensive process validation.” Table 4 gives the biosimilar products in the Indian market (Undela K, 2012).

India Vs China

India’s current lead in biosimilars manufacturing can be attributed to quality control standards and regulatory legislation. In addition, the high English proficiency among recent Indian graduates entering the field is also a contributor. India is thus stronger than China with respect to biosimilar market. However, with the evolving regulatory structure and lower wages of workers in China as compared to India, China is expected to overtake India’s position as the leader in biologic market by 2015 (Brown C et al., 2009).

Challenges In The Way of Biosimilars

Various challenges impede the growth of
biosimilars in the pharmaceutical market. It may be possible to tackle these problems but the effectiveness of regulations is not assured since creating guidelines that apply across all classes of biosimilars is difficult (Roger SD et al., 2000).

Complexity of Biologics

The biggest challenge in the development of biosimilars arises from the fact that biologics are more complex than small molecule and chemically synthesized drugs. Therefore, in contrast to ‘traditional’ small-molecule generics they are “similar” but not identical to the innovator biologic.

Generic drugs are chemically and therapeutically equivalent to branded, original chemical drugs whose patents have expired. There are various differences between chemical drugs and biologics along with those between chemical generics and biosimilars (Table 5) (Sekhon BS et al., 2011). Generic drugs are approved through a simplified registration procedure, the abbreviated new drug application (ANDA), with the demonstration of bioequivalence. However, the same standards cannot be applied for the development and evaluation of biosimilars.

Variability in characteristics of biosimilars

The molecular weight of biologics is 100 to 1000 times larger than small molecule chemical drugs. They possess fragile three-dimensional structure which is difficult to define by analytical tools (Roger SD, 2006). The characteristics of biologics are largely determined by their manufacturing process. Different manufacturing processes use different cell lines, protein sources, extraction and purification techniques, which result in heterogeneity of biologics. Even minor differences in cloning, fermentation or purification alter properties of biologics. It may be possible to mimic the initial amino acid sequence (primary structure), but analysis of structure reveals local folding (secondary structure) and subsequent global folding (tertiary structure). This occurs via various hydrogen and disulphide bonds. Oligomerization and modification of the protein primary sequence or glycosylation patterns is also observed (Roger SD, 2006; Schellekens H, 2009). Some biologics also exhibit quaternary structure, which is the stable association of two or more polypeptide chains into a multi-subunit structure, and this may further alter activity, duration of action, stability, pharmacokinetics, safety, immunogenicity and other properties (Roger SD, 2006).

Specific manufacturing processes, validation and full characterization of proteins are generally a company’s intellectual property and it becomes difficult for another manufacturer to reproduce a biologic similar enough to the original innovator product, based only on the patent or published data (Blackstone E et al., 2012). A classic example to illustrate that the safety profile of a biosimilar will not be identical to that of the reference product is the biosimilar growth hormone “Valtropine” that has different precautions and warnings than its reference product “Humatrope”. This may be a consequence of use of different cell lines (Undela K, 2012). All the heterogeneities between biosimilars and innovator biopharmaceutical have an impact on patient safety.

Shortcomings of characterization tools

Characterization of biosimilar product via analytical techniques is possible. However, physicochemical properties are assessed by techniques like MS in which extraction is required. This could possibly induce a change in physicochemical or structural properties of the material and hence influence comparability with reference innovator biologic (Cai XY et al., 2013).

Also it is not always feasible to assess the drug’s potency with bioassays. Moreover, bioassays themselves don’t have a universal standard and this leads to further variability. Due to lack of a reference standard for bioassays and the variability in binding assay results no clear guidelines can be set (Roger SD, 2006). Hence, there is also a lack of appropriate investigative tools.

Resources for fulfilling Regulatory requirements

It is claimed that ‘the process is the product,’ hence biosimilars can never be bio-identical with the innovator’s biologic (Roger SD, 2006). Thus, to obtain marketing authorization, the biosimilar should be considered in general as a new product that needs full documentation concerning quality, safety and efficacy. Small proteins such as insulin and calcitonin, which have very well-known properties and have been produced for many years, might be exempt from this rule (Schellekens H, 2004). The registration of biosimilars requires more data than for generics, and manufacturers have to demonstrate efficacy and safety via extensive pre-clinical and clinical studies. Data gathered from assessment of key similarities and differences between innovator biologic and biosimilar must also be submitted (Peres BC et al., 2012). Thus the registration of biosimilars is a costly and time-consuming process. Furthermore, the EMEA requires also post-marketing safety studies to observe immunogenicity and to establish rigorous pharmacovigilance programs (Schellekens H, 2009). This increases resources required.

Immunogenicity

Immunogenicity is the capability of a specific substance to induce the production of antibodies in the human body. All biologics demonstrate a greater capacity to elicit such an immune reaction because they are polypeptides or proteins. In many patients, such a
response does not lead to any clinical consequences. However, there is potential for general immune reactions like allergy and anaphylaxis. In addition, they may cause reactions which lead to a loss of effect from the medicine or rarely reactions which cause an enhancement of activity. The most impressive complications of antibody production arise when the antibodies cross-react with an endogenous factor that has a unique and important biological function, thus disturbing body homeostasis (Schellekens H, 2004).

Immunogenicity may be influenced by factors relating to the drug itself e.g. manufacturing process and formulation, and also by factors related to the patient, disease or treatment e.g. route of administration or depressed immune response in cancer patients (Brown C et al., 2009). Immunogenicity needs to be monitored during every stage of development of biosimilars and throughout its life using bioassays. It should be noted that responses are highly individual and that bioassays are not standardized. Different laboratories use their own assay format, and no international standards are available. Sampling time can also influence results because the product in circulation can mask the presence of antibodies (Schellekens H, 2004).

Substitution or interchangeability

Substitution of chemical drugs by generic versions is a common practice followed by pharmacists. It must be avoided in the case of biologics (Niederwieser D et al., 2011). Biosimilar products are never identical and immune responses against them are highly unpredictable (Nowicki M, 2007; Roger SD et al., 2007) hence, selection of a substitute must be done carefully.

Intellectual property issues

Biosimilars raise two major problems associated with patents. The first relates to the actual R&D process leading to the creation of a new drug and the second to litigation. The fact that a biosimilar will not be required to be the “same” as the innovator biologic potentially allows biosimilar companies to “design around” relevant patents, so that they create a product that is (1) sufficiently similar to rely, at least to some extent, on the marketing approval of the innovator biologic, yet (2) sufficiently different to avoid patent infringement. Thus, biosimilars could reach the market well ahead of the expiration of patents belonging to innovator biologics and at much considerably lower costs. As a result, patent protection may not be as robust for biologics as it is for small-molecule chemical drugs. Also, a biologic can hold several patents, for example, not only on the active ingredient and route of administration, but also on the development and manufacturing technology. Hence, disputes over patent infringement may become even more complicated. (Chu R et al., 2009).

Counter-steps of innovators

Chemical generics lower drug prices by as much as 90 per cent. On the other hand, biosimilars are only 10 to 20 per cent less than the branded biologics owing to the expenses. Therefore, an innovator biologic could reduce its price by a fairly small amount, perhaps 10 to 20 per cent and this will discourage buyers from switching to the biosimilar (Blackstone EA et al., 2012).

Efforts to Pave the Way For Biosimilars

Nurses, hospital pharmacists, dispensing pharmacists, prescribers, and patients must all be aware of and educated about biosimilar for avoiding substitution or interchangeability related problems and to consider in the developing countries, whereas patient safety and brand loyalty may be deciding factors in developed countries (Roger SD et al., 2007).

Pharmacovigilance as a solution

All European pharmaceutical companies are legally required to monitor the use and effects of all their medicines. They must have systems in place to detect, assess, understand, communicate and prevent any adverse reactions or any other medicine related problem. The science and activities of these processes are known as ‘Pharmacovigilance’ (Brown C et al., 2009). As a part of the pharmacovigilance activities, the type and level of immune response should be examined after the product is authorized and marketed (Schellekens H, 2004). This forms a component of a robust risk management plan.

EMEA requires biosimilars to have a unique INN to facilitate prescribing and dispensing and also to aid in precise pharmacovigilance (Nowicki M, 2007). Biosimilar manufacturers should exhibit a patient-focused commitment to upholding the highest standards. Biologics manufacturers should not adopt identification mechanisms that risk confounding pharmacovigilance data with those of other manufacturers. Reliable and rapid tracing of adverse drug reactions (ADRs) to the actual biologic product is a must. Biologics have a unique risk profile compared with traditional pharmaceuticals since ADRs can occur as a result of the interaction of specific structural differences with the physiology of individual patients. Since these structural differences can be process-specific, even highly similar biologics could diverge in terms of prevalence or severity of ADRs. Without traceability, adverse safety outcomes related to differences in quality could go unrecognized or undetected, thus increasing the likelihood that emerging adverse events would not be recognized as being uniquely related to a particular
product. It will not be possible to do accurate post-marketing surveillance unless biosimilars are clearly differentiated from the innovator biologic (Roger SD, 2006). If the relationship between a significant event and a particular product is unrecognized, appropriate clinical, manufacturing and, potentially, regulatory actions cannot be taken.

**Promising Future of Biosimilars**

In 2011, for the first time, the major regions (e.g., EU, US, Japan, Canada) gave pathways for biosimilar product approval and many of the largest emerging markets (e.g., South Africa, Brazil, India) either already have finalized or are in the process of drafting biosimilar guidelines. Importantly, since 2010 the World Health Organization has been offering a finalized guidance document on biosimilar approval standards that is intended to be used as a basis for regulatory agencies to set local requirements. With the advancements in technology, a higher standard of analytical similarity of biosimilar to their reference innovator biologic will be available in future. Advances in protein engineering, understanding of critical quality attributes and the development of high-throughput, high-resolution technologies for screening of process conditions will enable this. Technology now allows high throughput screening of cell lines and process variables. Highly sensitive pharmacology and an informative pharmacokinetic equivalence evaluation have facilitated clinical trials in evaluating the equivalent efficacy and non-inferior safety of the biosimilar product (Miletich J et al., 2011).

Biotechnology has advanced to such an extent that in some cases accurate copies of an innovator’s biologic can be created. This can be done by using microbial cell production rather than mammalian cell lines. In particular, proteins created through microbial fermentation in *Escherichia coli*, which have no post-translational modifications. They can be produced cheaply and easily with high purity and reliability (Roger SD, 2006).

To tackle immunogenicity, computer algorithms can be used to design less immunogenic proteins (Schellekens H, 2009).

Quality, safety and efficacy of biosimilars may be assessed by HPLC, gel electrophoresis, cell-based bioassay, FTIR, MS/MS, MALDI-TOF, spectroscopy and such other methods to name a few (Sekhon BS et al., 2011).

Foreign clinical data often helps assure that drugs are evaluated in diverse but representative patient populations before approval. A unique challenge, however, will be in defining a “global” reference product and demonstrate that comparator products sourced from various regions are suitable to represent the reference product that a patient in a given region might receive (Miletich J et al., 2011).

### Table 1. Approved biosimilars G-CSF in Europe

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Common name (INN)</th>
<th>Biosimilar sponsor</th>
<th>Reference product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biograstim®</td>
<td>Filgrastim</td>
<td>CT Arzneimittel GmbH</td>
<td>Neupogen®</td>
</tr>
<tr>
<td>Filgrastim ratiopharm®</td>
<td>Filgrastim</td>
<td>Ratiopharm GmbH</td>
<td>Neupogen®</td>
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<tr>
<td>Ratiogranstim®</td>
<td>Filgrastim</td>
<td>Ratiopharm GmbH</td>
<td>Neupogen®</td>
</tr>
<tr>
<td>Tevagranstim®</td>
<td>Filgrastim</td>
<td>Teva Generics GmbH</td>
<td>Neupogen®</td>
</tr>
<tr>
<td>Zarzio®</td>
<td>Filgrastim</td>
<td>Sandoz</td>
<td>Neupogen®</td>
</tr>
<tr>
<td>Filgrastim HEXAL®</td>
<td>Filgrastim</td>
<td>Hexal</td>
<td>Neupogen®</td>
</tr>
<tr>
<td>Nivestim®</td>
<td>Filgrastim</td>
<td>Hospira</td>
<td>Neupogen®</td>
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### Table 2. Indian Regulatory Authorities involved in the approval of biosimilars

<table>
<thead>
<tr>
<th>Committee</th>
<th>Department</th>
<th>Responsibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Institutional Biosafety Committee (IBSC)</td>
<td>Institutions</td>
<td>Training of personnel on Biosafety and instituting health monitoring program for laboratory personnel.</td>
</tr>
<tr>
<td>Review Committee For Genetic Manipulation (RCGM)</td>
<td>Department of Biotechnology - Ministry of Science &amp; Technology</td>
<td>Monitors all research scale activity and approval for non-clinical studies</td>
</tr>
<tr>
<td>Genetic Engineering Advisory Committee (GEAC)</td>
<td>Ministry of Environment</td>
<td>Environmental safety for large-scale operations of Live Modified Organism (LMO) based products</td>
</tr>
<tr>
<td>Drug Controller General of India (DCGI)</td>
<td>Ministry of Health</td>
<td>Product safety and efficacy &amp; Clinical Trial &amp; Marketing approval for Biotech drugs</td>
</tr>
<tr>
<td>Food &amp; Drugs Control Administration (FDCA)</td>
<td>State government body, Under Ministry of Health</td>
<td>Approves plant &amp; ensures cGMP.</td>
</tr>
</tbody>
</table>
Table 3. The regulatory pathway for approval of biosimilars in India

<table>
<thead>
<tr>
<th>Stage</th>
<th>Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product development</td>
<td>• Approval needed from Institutional Bio-safety Committee (IBC)</td>
</tr>
<tr>
<td></td>
<td>• Approval needed from Department of Biotechnology (DBT)</td>
</tr>
<tr>
<td>Animal toxicity studies</td>
<td>• Protocol to be designed as per schedule Y, approved by DBT</td>
</tr>
<tr>
<td></td>
<td>• Study need to be conducted in GLP accredited laboratories</td>
</tr>
<tr>
<td></td>
<td>• Report need to be approved by DBT</td>
</tr>
<tr>
<td>Clinical trial</td>
<td>• Protocol need to be approved by DCGI (followed by DBT approves the toxicity study report)</td>
</tr>
<tr>
<td></td>
<td>• Manufacturing license is needed for CT batch manufacturing (along with WHO GMP certificate)</td>
</tr>
<tr>
<td></td>
<td>• The protocol need to be approved by Institutional Ethics Committee</td>
</tr>
<tr>
<td></td>
<td>• Any deviation need to be approved by DCGI and DSMB</td>
</tr>
<tr>
<td>Marketing and manufacturing license</td>
<td>• CT report to be submitted to DCGI</td>
</tr>
<tr>
<td></td>
<td>• The dossier (in CTD format) need to be approved by DCGI</td>
</tr>
<tr>
<td></td>
<td>• Manufacturing license should be issued after inspection of the facility</td>
</tr>
<tr>
<td>Post approval commitments</td>
<td>• Mandatory PMS (at least for 4 months) PV study (throughout)</td>
</tr>
<tr>
<td></td>
<td>• Every 6 months safety reporting to DCGI for first 2 years (PSUR)</td>
</tr>
<tr>
<td></td>
<td>• Any process change need to be approved by DCGI</td>
</tr>
</tbody>
</table>

Table 4. Biosimilar products in India

<table>
<thead>
<tr>
<th>Biosimilar</th>
<th>Company</th>
<th>Product Name</th>
<th>Year of Launch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Wockhardt</td>
<td>Wosulin</td>
<td>2003</td>
</tr>
<tr>
<td></td>
<td>Biocon</td>
<td>Insugen</td>
<td>2004</td>
</tr>
<tr>
<td></td>
<td>Shreya Life Sciences</td>
<td>Recosulin</td>
<td>2004</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>Hindustan Antibiotics</td>
<td>Hemax</td>
<td>2000</td>
</tr>
<tr>
<td></td>
<td>Emcure</td>
<td>Epofor</td>
<td>2001</td>
</tr>
<tr>
<td></td>
<td>Wockhardt</td>
<td>Wepox</td>
<td>2001</td>
</tr>
<tr>
<td></td>
<td>Ranbaxy</td>
<td>Ceriton</td>
<td>2003</td>
</tr>
<tr>
<td></td>
<td>Intas Pharmaceuticals</td>
<td>Epofit &amp; Erykine</td>
<td>2005</td>
</tr>
<tr>
<td></td>
<td>Shantha Biotechnics</td>
<td>Shanpoietin</td>
<td>2005</td>
</tr>
<tr>
<td>Hepatitis B vaccine</td>
<td>Shantha Biotechnics</td>
<td>Shanvac B</td>
<td>1997</td>
</tr>
<tr>
<td></td>
<td>Bharat Biotech</td>
<td>Revac B</td>
<td>1998</td>
</tr>
<tr>
<td></td>
<td>Panacea Biotech</td>
<td>Enivac HB</td>
<td>2000</td>
</tr>
<tr>
<td></td>
<td>Wockhardt</td>
<td>Biovac-B</td>
<td>2000</td>
</tr>
<tr>
<td></td>
<td>Serum Institute of India</td>
<td>Gene Vac-B</td>
<td>2001</td>
</tr>
<tr>
<td></td>
<td>Biological E</td>
<td>Bevac</td>
<td>2004</td>
</tr>
<tr>
<td>Granulocyte colony</td>
<td>Dr Reddy’s Laboratories</td>
<td>Grastim</td>
<td>2001</td>
</tr>
<tr>
<td>stimulating factor</td>
<td>Intas Pharmaceuticals</td>
<td>Neukine</td>
<td>2004</td>
</tr>
<tr>
<td>Streptokinase</td>
<td>Bharat Biotech</td>
<td>Indikinase</td>
<td>2003</td>
</tr>
<tr>
<td></td>
<td>Shantha Biotechnics</td>
<td>Shankinase</td>
<td>2004</td>
</tr>
<tr>
<td></td>
<td>Cadila Pharmaceuticals</td>
<td>STPase</td>
<td>2004</td>
</tr>
<tr>
<td>Interferon alpha-2b</td>
<td>Shantha Biotechnics</td>
<td>Shanferon</td>
<td>2002</td>
</tr>
<tr>
<td>Rituximab (MAb)</td>
<td>Dr Reddy’s Laboratories</td>
<td>Reditux</td>
<td>2007</td>
</tr>
<tr>
<td>Anti- Epidermal Growth Factor (MAb)</td>
<td>Biocon</td>
<td>BioMAB-EGFR</td>
<td>2006</td>
</tr>
</tbody>
</table>

Table 5. Differences between small chemical drugs and Biologics

<table>
<thead>
<tr>
<th>Small-molecule drug</th>
<th>Biologics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product related differences</strong></td>
<td><strong>Biotechnologically produced by host cell lines</strong></td>
</tr>
<tr>
<td>• Produced by chemical synthesis</td>
<td>• High molecular weight</td>
</tr>
<tr>
<td>• Low molecular weight</td>
<td>• Complex physiochemical properties</td>
</tr>
<tr>
<td>• Well-defined physiochemical properties</td>
<td>• Sensitive to heat and shear (aggregation)</td>
</tr>
<tr>
<td>• Stable</td>
<td>• Heterogeneous mixture, broad specifications which may change during development, difficult to standardize</td>
</tr>
<tr>
<td>• Single entity, high chemical purity, purity standards well established</td>
<td>• Usually administered parenterally</td>
</tr>
</tbody>
</table>
administration
• Rapidly enters systemic circulation through blood capillaries
• Distribution to any combination of organ/tissue
• Often specific toxicity
• Often non-antigenic

• Larger molecule primarily reach circulation via lymphatic system, subject to proteolysis during interstitial and lymphatic transit
• Distribution usually limited to plasma and/or extracellular fluid
• Mostly receptor mediated toxicity
• Usually antigenic

Manufacture related differences
• Completely characterized by analytical methods
• Easy to purify
• Contamination can be generally avoided, is easily detectable and removable
• Not affected by slight changes in production process and environment.

• Difficult to characterize
• Lengthy and complex purification process
• High possibility of contamination, detection is harder and removal is often impossible
• Highly susceptible to slight changes in production process and environment

Fig 1. The timeline for development of biosimilar

CONCLUSION

Biologics will become an important part of the future healthcare landscape. Biologics and properly regulated biosimilars will increasingly become available. The development of biosimilars represents a significant opportunity for generic firms interested in entering the marketplaces for biotechnologically produced drugs. Without the necessity of undertaking costly full-scale R&D activities, they can manufacture and market recombinant proteins. However, success in the biosimilars industry will require significant capital investment and in-house experience. Biosimilars manufacturers have to face higher costs for manufacturing, clinical development, registration and product marketing compared to classic generics.

The establishment of a globally harmonized regulatory framework is important. India and Argentina currently apply standard generic drug authorization provisions to biosimilars. On the other hand, Australia, Bulgaria, Canada, Chile, China, Croatia, European Union, Israel, Japan, Mexico, Serbia, Switzerland, Taiwan, Turkey and Ukraine have already established special provisions. Egypt, New Zealand, Oman, Panama and Russia do not permit any application for biosimilars. The insufficient power supply and storage conditions in India pose a big challenge to biosimilar stability. Moreover, the market for resale of expired drugs with compromised safety and efficacy is mushrooming in India. This may be a safety concern for biosimilars. Developing specific guidelines is important for approval of biosimilars in India. Various aspects like quality of the product, pharmacovigilance, immunogenicity, etc. must be touched in the guidelines with special emphasis on immunogenicity studies. Some outstanding issues like naming, substitution and labeling need to be resolved (Schellekens H, 2009).

A quality biosimilar is that which exhibits the same concentration and equivalent potency to, the reference biologic. This assures that the biologic provides a similar clinical effect at a given dose. This will bring choices to patients, prescribers and payers in many markets without asking them to make trade-offs between cost and benefit risks of a biologic (Miletich J et al., 2011). For healthcare purchasers and national pricing and reimbursement authorities, biosimilars offer an equivalent and less expensive alternative to reference biologics. This means that more patients can be treated within the same limited budget.

REFERENCES

Bruckner M, Resch A, Pham-Thi TB. Biosimilars- Emergence of a third market dynamic between original products and generics. Accenture. 2009; 3-8.


