

Biosimilars: Current Scenario and Challenges in India

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ABSTRACT

For a long period of time, biologics have been a major part of the pharmaceutical sector in providing treatment for most complex diseases like cancer, Alzheimer's disease, etc. With their patent expiration, a wide scope of opportunities has been unleashed for their replication. For the low molecular weight biologics, generics are preferable and safe option, whereas the large sized biologics being inaccessible for their price have led to the introduction of a new genre of medicine, Biosimilar. Biosimilar is designed with the intent to treat a patient in the same way as an existing biologic therapy. They are not the exact replicas of their innovator drugs. They are derived protein having immunogenic reaction and risk of adverse events. Despite the hurdles, biosimilar offer promising beneficial and cost effective option, if allowed to be understood by physicians and patients.

Keywords: Biosimilar, biologics, generics, replicas, cost effective.

INTRODUCTION

The field of medicine has been able to achieve a new class of medicine, especially with the advancement in biotechnology¹⁻². These types of medicine are large sized molecules that are made in the bodies of living organisms by addition of DNA to cells. The cells further copy or translate this piece of DNA into a protein and thus a biologic medicine is created. In comparison to chemical generics these are about 200-1000 times larger in size³⁻⁵. These products being highly complexed in comparison to chemical drugs, are in fact polypeptides or glycoproteins or nucleic acids⁶⁻⁷. Live cell lines are employed in the production of biologics which is why their reproduction is a difficulty. This is the reason biologics once manufactured are very hard to replicate exactly. The term biosimilar emphasize the difference

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(Received 22 September 2017, accepted 23 October 2017)

in two products, similar to the innovator biologics but not their exact copy. In the past few years a number of biopharmaceutical patents have expired including granulocyte colony stimulating factors [G-CSFs], erythropoietin, interferons and human growth hormone. This has given way to the production of Biosimilar. When compared to their innovator biologics, few structural differences were found but however were clinically insignificant for consideration. Biosimilar, have the liberty to not undergo the same gruesome approval procedures as biologics which reflects in its cost, but in comparison to generic drugs they are still costlier⁸⁻⁹.

Biologics-characteristics, significance and use

Biologics is a term to refer to the most developed and significant area of biotechnological products that include viruses, allergenic, somatic cells, blood products, tissues, gene therapy and recombinant therapy proteins. With biologics, some of the milestones in therapeutic medicine that were not thought to be achieved are now in existence that include production of proteins with a special set of functions (e.g., fligrastim) and monoclonal antibodies that can target specific molecules (e.g., adalimumab)¹⁰.

The foundation of biologic medicines lies in recombinant DNA technology, which involves genetically engineering a cell that is an intricate, sensitive process and often specific to a particular medicine. The quality and efficacy of the biopharmaceutical at the final production stage depends on various factors such as, type of expression system, e.g. bacteria, yeast and mammalian cells, growth conditions offered, purification processes, storage and transport protocols undertaken. During cell synthesis, certain modifications are bound to occur such as, glycosylation, phosphorylation, sulphation, methylation, acetylation and hydroxylation which can alter the therapeutic potential of the drug. Such modifications need to be calculated as they can be the reason for production of a million variants of drugs¹¹.

Biologics are very sensitive to factors such as temperature and pH, which makes them hard to characterize and produce on large scale. Any minor modifications may lead to alteration in characteristics and change in structure, stability or other qualities of the final product. These have the possibility to affect the treatment safety, efficacy and shelf life and also increase the risk of immunogenic reactions.

In the present time, some of the most important medicines are biologics which include albumin, monoclonal antibodies, human insulin used for burns or liver failure, cancer and diabetes respectively.

Some other biologics include cloned proteins that occur naturally and erythropoietin in treatment of chronic anemia by stimulation of red blood cell production. In the treatment of some very critical conditions like cancer, rheumatoid

arthritis (RA), psoriasis and multiple sclerosis biologics have been observed to be most effective¹².

Biosimilar

Biosimilar can be said to be the latest biopharmaceutical agent that are 'similar' but in many aspects cannot be considered 'identical' to its reference product. They are synonymously also called Subsequent Entry Biologics (SEB) and Follow on Biologics. Post expiration of the patent(s) for these primarily approved biopharmaceuticals, other biotech and pharma companies acquire the chance to copy and market these biological drugs. These along with generic medicines can prove cost effective for patients and other sectors of society.

Biologic medicines exhibit both structural and molecular complexity. For the development and manufacture of high quality Biosimilar an intrinsic scientific knowledge and manufacturing expertise is required. Initially a cell line is chosen for the production of right clone. Thorough understanding of reference drug and its pharmacodynamics are the major criteria for Biosimilar development.

A Biosimilar is required to show similarity with reference biologic on the basis of:

1. Analytical (testing in a lab for structural/physical similarity),
2. Non-clinical (testing for function/activity/toxicity) and
3. Clinical data (testing in humans for safety and efficacy) in terms of structural characteristics, safety and efficacy.

How similar are biosimilar to biologics?

Biosimilar are not generic alternatives of innovator drugs nor can they be the exact duplicates of their innovator product. A Biosimilar and its reference cannot be entirely identical due to their differing manufacturing processes, but to qualify the approval process the protein sequence has to be same and structural alterations to a minor extent can be accepted¹³⁻¹⁵. It is critical to understand the differences and to demonstrate that they are not clinically meaningful and thus can be expected to be as safe and effective as the reference product for that approved condition of use.

The explicit details of the manufacturing processes employed in innovator drug production are a patented source and not always accessible. Thus, for Biosimilar to be exactly duplicated as their reference protein is impossible. Also the fact remains that detecting the protein characteristics require stringent analytical techniques, lack of which makes a thorough study of biopharmaceutical product difficult. Thus, regulatory guidelines have to be abided and pharmacovigilance is mandatory.

Although innovator biologic products and Biosimilar are both proteins by nature, they both tend to possess immunogenic potential. However Biosimilar can have more adverse drug reaction episodes of the immunogenicity type than reference products as they do not go through the exact same regulatory approval when compared to innovator drugs¹⁶.

Biosimilar versus generics¹⁷⁻¹⁸

A generic drug is a chemically and therapeutically equivalent entity of a low molecular weight drug whose patent has expired. Biologics and Biosimilar are produced from live cells. On the other hand small molecule drugs and generics are produced by chemical / synthetic method. These discrepancies show that Biosimilar are not equal to generics. For a better understanding, the significant differences that exist between biologics and traditional small-molecule drugs in terms of basic chemical structure and manufacturing processes should be studied.

Chemical generics are small but well-defined molecules that can be generalized as chemical structures that are stable by nature. On the other hand, biopharmaceuticals are large peptides or proteins that have complex structural makeup. They are primarily made of amino acid sequence that should correspond to the traditional pharmaceutical. They have a three-dimensional structure which is highly sensitive to a lot of factors and need care while handling.

A finished generic drug can undergo chemical analysis to identify its various components whereas it is not just difficult but sometimes impossible to characterize a biologic and identify its components in a laboratory which explains its unique nature for many of its features may remain unknown.

Manufacturing differences between Biosimilar and generics¹⁹⁻²⁰

Generic low molecular weight drugs are synthesized chemically by a combination of known reagents or ingredients in a series of controlled and predictable reactions. Biopharmaceuticals or Biosimilar are prepared in a living system that also secretes many other substances other than the required protein.

Therefore, generics can be replicated in an exact manner and they achieve an atomically identical structure to the reference drug. Biologics being complex will exhibit some physical and chemical differences. The variation in the production processes will also bring about some modifications (e.g. purification methods, post-traditional modification as glycosylation or sialylation, tertiary or quaternary structures)²¹. Apart from the above two major differences, there also exist some other characteristic differences that are listed below in Table 1.

Table 1. Characteristic differences between generics and biosimilar

Property	Generics	Biosimilar
Molecular weight	< 500-900 Daltons	> 140,000 Daltons
Manufacture	Synthesized in laboratory or extracted from natural sources	Manufactured from genetic material of living cell cultures or DNA technologies
Adverse immune reaction	Lower potential and predictable	Higher potential and unpredictable
Composition	Active ingredients that are identical to the innovator product	Active proteins or peptides that is not identical but similar to innovator drug to a questionable extent.
Approval requirements	Small clinical trials mostly in healthy volunteers	Phase 3 onwards extensive clinical trials in patients.

Development of Biosimilar

The development of Biosimilar is a highly skilled, multi-step process that requires extensive understanding of the reference drug product. The multi-step process involved in the assessment and creation of a Biosimilar are given as follows.

Creating and Producing a Biosimilar



Clinical studies

A first stage in healthy volunteers or patients to test that the body processes the biologic in the same way as the reference product and,

A second stage in patients to test that the Biosimilar works with similar level of efficacy and safety as a reference product.

Comparison between the reference product and biosimilar

Lab testing and clinical testing of drug on patients are performed for bringing out a comparative study of the Biosimilar produced to its reference product. However there still exists an insufficient analytical testing system that lacks the ability to predict certain activity or safety reactions in patients.

Challenges in biosimilar development

The complex and variable nature of biologics and biosimilar presents numerous challenges for manufacturers and also the regulatory bodies such as European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA) and New India Guidelines that are responsible for approval process²²⁻²⁴. Several such issues include as follows.

Naming and labeling

Each Biosimilar medicine has given a unique and easily recognizable International Non-proprietary Name (INN). This naming program is recommended majorly by WHO with the intention to identify a drug by its active pharmaceutical ingredients. This name is a public property and can avoid confusion among prescribers, pharmacists or dispensers. Pharmacovigilance becomes easy by reporting the specific name of the medicine in case of an adverse event. Substitution should be avoided for both biologics and Biosimilar as this can lead to a delayed adverse event reporting because substitution leads to lack of traceability and tracking of the drug dispensed.

Safety and efficacy issues / Immunogenicity

The large molecular weight and size along with its complex nature, makes the immune system within a body recognize the biologic medicine, giving way to the possibility of a range of immunologic responses. This can result in consequences affecting the efficacy (neutralizing antibodies) and may give rise to anaphylactic or infusion reactions²⁵. Small changes in any of the production steps of biosimilar can be a reason for alternations in cell behavior and can eventually affect the structural detailing or quality of the product. These changes can in turn disturb the shelf life of the products by interfering with its safety and efficacy, also possibly causing an immune response. Differences in age, gender and subsequent medicines taken can also affect patient response and needs consideration²⁶.

Quality issues

The manufacturing methods of Biosimilar have concerns about the quality and standards. The manufacturing method for a biosimilar should have the same quality requirements as any new biologic manufacturers and show that their process can produce a high-quality product. The method must include the scientific knowledge by which Biosimilar manufacturer may have access to advanced processes in comparison to the ones used for older originator products.

Substitution issues

The rulings and purpose for substituting biosimilar is different than generics. Generic drugs chemically synthesized can be substituted with their original drugs because they are identical, have the same therapeutic effect and are cost effective. However, in the case of biosimilar such irrational substitution can lead to adverse events and even failure of the intended therapy. This information is significant for a pharmacist and prescriber because a pharmacist can substitute a prescribed reference drug with a biosimilar or vice versa. In case of an adverse event, lack of accuracy in the documentation of the product dispensed to the patient can prove a hassle in pharmacovigilance assessment.

Issues related to regulatory approval

Adequate data of safety and efficacy of post animal and human study, pharmacovigilance and risk management data have to be submitted by the innovator companies and biosimilar producers to the US FDA and EMA for their approval. According to FDA biosimilar guidance announced by US FDA on February 9th, 2012, there exist lists of factors that need to be considered to demonstrate similarity of a biosimilar product to its reference drug. These include an intrinsic understanding of the manufacturing processes, mechanism of action, pharmacodynamics as well as pharmacokinetic studies including the immunogenicity potential and comparison of structural features of the two. Biosimilar do not undergo very extensive clinical trials but have to submit relevant data to be considered equivalent to a reference drug in terms of safety and clinical efficacy.

Pharmacovigilance

All biologic medicines, including Biosimilar, present at least some risk of an unwanted immune response to the medicine, where the patient reacts against the proteins in the medicine. The timely reporting of this and other adverse events is important. The difference that exists in Biosimilar inherently could be the cause for adverse events that might get overlooked at the time of Biosimilar approval.

In the pre-marketing period only a fixed number of patients receive the product which is why a very profound or rather extensive pharmacovigilance program is

required for distinguishing immunogenic reaction episodes. Standard methods for detection of immunogenic reactions should be adapted. Lack of validated methods may not give information about the extent of adverse reaction and their management. The ADR monitoring should include complete details of the drug received, whether a reference or Biosimilar, proprietary name and International Non-proprietary Name (INN) along with the exact dosage administered²⁷.

Biosimilar in India

Biosimilar in India are defined as: “A biological product/drug produced by genetic engineering techniques and claimed to be ‘similar’ in terms of quality, safety, and efficacy to a reference innovator product, which has been granted a marketing authorization in India by a competent authority on the basis of a complete dossier, and with a history of safe use in India²⁸.”

Here are few factors that facilitate the development and uptake of Biosimilar in India.

- Patent enforcements undertaken by manufacturing companies are guarded by poor laws that give opportunities for domestic biologic manufacturers and private sector partnerships to promote Biosimilar development.
- There are less strict regulatory requirements and low R&D costs, domestic biologics are priced much lower in India compared to originators.
- The low price of Biosimilar compared to originator brands is restricted by limited health insurance coverage and therefore there still exists poor access to biologic drugs.
- Issues regarding the quality and safety of some domestically manufactured Biosimilar and lack of patient education remain a concern among patients and physicians²⁹⁻³⁰.

Indian regulations and guidelines on biosimilar production

In June 2012, the Department of Biotechnology (DBT) has announced The New India Guidelines, “Draft Guidelines on Similar Biologics: Regulatory Requirements for Marketing Authorization in India.” These guidelines mention the regulatory pathway for a similar Biologic to declare to be similar to an already existing Reference Biologic.

The guidelines mention regarding manufacturing process, safety and efficacy and quality aspects for similar biologics. The guidelines also mention the pre-market regulatory requirements along with comparability exercise for quality, preclinical and clinical studies and post market regulatory needs for Similar Biologics.

The Similar Biologics are regulated as per the Drugs and Cosmetics Act, 1940, the Drugs and Cosmetics Rules, 1945 (as amended from time to time) and Rules for the manufacture, use, import, export and storage of hazardous microorganisms / genetically engineered organisms or cells, 1989 (Rules, 1989) notified under the Environment (Protection) Act, 1986.

Various applicable guidelines are as follows:

- Recombinant DNA Safety Guidelines, 1990
- Guidelines for generating preclinical and clinical data for rDNA vaccines, diagnostics and other Biologicals, 1999
- CDSCO guidance for industry, 2008:
 - Submission of Clinical Trial Application for Evaluating Safety and Efficacy
 - Requirements for permission of New Drugs Approval
 - Post approval changes in Biological products: Quality, Safety and Efficacy Documents
 - Preparation of the Quality Information for Drug Submission for New Drug Approval: Biotechnological/Biological Products
- Guidelines and Handbook for Institutional Biosafety Committees (IBSCs), 2011
- Guidelines on Similar Biologics: Regulatory Requirements for Marketing authorization in India 2012

Competent Authorities in the Approval Process of Biosimilar

a) Institutional Biosafety Committee (IBSC)

A person in any research institution who is handling the hazardous microorganisms and / or genetically altered organisms need to constitute the IBSC. The main objective of IBSC is to ensure the biosafety and review the applications to be recommended to RCGM. It is also responsible to review and authorize firm for exchange of the above-mentioned organisms for the purpose of research.

b) Review Committee on Genetic Manipulation (RCGM)

The main role of RCGM is to authorize import / export for research and development, exchange of genetically modified organisms for the purpose of research and development and review of data up to preclinical screening.

c) Genetic Engineering Appraisal Committee (GEAC)

Under the Ministry of Environment and Forests (MOEF) the GEAC works as a statutory body to review the research proposals and approve the activities for the

final drug product which contains the genetically modified organisms / living modified organisms.

d) Central Drugs Standard Control Organization (CDSCO)

The main function of CDSCO is to grant the import / export license, clinical trial approval and giving permission for marketing and manufacturing. The State Food and Drug Administration works along with CDSCO for issuing the licenses to the manufacturer of similar biologic in India. Import of drugs for examination, test and analysis for research and development is done by zonal CDSCO.

Factors that favor and withhold biosimilar use in India

Various factors *contribute* in the development and uptake of Biosimilar in India. These include:

- Poor patent enforcement in India provides opportunities to obtain approval for domestically manufactured Biosimilar that are ruling the Indian Biologics market.
- Less stringent regular requirements, lack of monitoring of laws and low R&D costs promotes Biosimilar development. Phase 1-2 clinical trials are not required for copying biologics if pharmaco-equivalence is proved whereas phase 3 trials can be performed on equal to or less than 100 patients. Also Biosimilar development takes approximately 8 years in the Europe, it only takes 3–5 years in India for a copy biologic. For Indian Biosimilar industry cost is a major advantage. In India to manufacture a Biosimilar molecule it need of US \$10 to 20 million when compared to developed countries which need US \$ 50 to 100 million. It shows that in India there is nearly 40% reduction in cost which makes it attractive place for Biosimilar manufacture³¹⁻³².
- Due to low development and manufacturing costs, domestic biologic manufacturers are able to sell their products at a heavy discount in the range 12- 74% in comparison to the original drug that is sold in Indian market. Such discounting forces the originators to reduce their price to retain their market share.
- Domestic and foreign companies owing to the commercial opportunity are trying to enter into the market of biosimilar. However, these companies face a major drawback for successfully developing, manufacturing and commercializing Biosimilar. This has drawn partnership as a solution. Such mutually beneficial collaborations help the source company with experience and resources whereas the partnering company benefits by establishing itself in the biologics market.
- However, if such drivers of development exist, on the other hand there are certain reasons that become *resistors* in the path of Biosimilar development. Some such are:

a) Low affordability of the comparatively expensive Biosimilar/biologics due to

lack of health insurance is a major drawback for obtaining therapeutic benefit. So majority of the patients fail to afford such expensive treatment options.

b) The physicians still hesitate to prescribe Biosimilar as an alternate to biologics. Moreover, there has been noticeable difference in the potency between several Indian Biosimilar compared to their reference products. Manufacturing processes being different introduces impurities that can pose a threat to the final product. In order to minimize the risk of immunogenicity prescribers often avoid any such substitution³³⁻³⁴. The Biosimilar which are produced in India after the amendment of “Similar Biologic guidelines” were shown in Table 2.

Table 2. Biosimilars produced in India after “Similar Biologics Guideline” which came into effect on 15 September 2012²⁹⁻³¹

Product name	Active substance	Therapeutic area	Approval/ launch date in India	Company
AbcixiRel	Abciximab	Angina, Cardiac ischemia	Apr-13	Reliance Life Sciences
Actorise	Darbepoetin alfa	Anaemia, Cancer, Chronic kidney failure	Jan-14	Cipla/Hetero
Adfrar	Adalimumab	Ankylosing spondylitis, Plaque psoriasis, Psoriatic arthritis, Rheumatoid arthritis, Ulcerative colitis	Jan-16	Torrent Pharmaceuticals
Bevacirel	Bevacizumab	Colorectal cancer	Jun-16	Reliance Life Sciences (Lupin)
CanMab	Trastuzumab	Breast cancer	Oct-13	Biocon
Cizumab	Bevacizumab	Colorectal cancer	Jun-16	Hetero
Darbatitor	Darbepoetin alfa	Anaemia, Cancer, Chronic kidney failure	2014	Torrent Pharmaceuticals
Etacept	Etanercept	Ankylosing spondylitis, Rheumatoid arthritis, Psoriatic arthritis, Psoriasis, Juvenile rheumatoid arthritis	Apr-2013	Cipla
Exemptia	Adalimumab	Rheumatoid arthritis	Sep-14	Zydus Cadila
Filgrastim	Filgrastim	Neutropenia	Oct-13	Cadila Pharmaceutical
Filgrastim	Filgrastim	Neutropenia	Mar-13	Lupin

Product name	Active substance	Therapeutic area	Approval/ launch date in India	Company
Folisurge	Follitropin alfa (follicle stimulating hormone)	Female infertility, Spermatogenesis in men	May-13	Intas Pharmaceuticals
Infimab	Infliximab	Ankylosing spondylitis, Crohn's disease, Psoriasis, Psoriatic arthritis, Rheumatoid arthritis, Ulcerative colitis	Sep-14	Epirus Biopharmaceuticals
Intacept	Etanercept	Ankylosing spondylitis, Juvenile idiopathic arthritis Psoriasis, Psoriatic arthritis, Rheumatoid arthritis	Mar-15	Intas Pharmaceuticals
MabTas	Rituximab	Lymphoma, Non-Hodgkin's Lymphoma	Feb-13	Intas Pharmaceuticals
Molgramostim	Recombinant human granulocyte macrophage colony stimulating factor (molgramostim)	Neutropenia	May-13	Zenotech Laboratories
Peg-filgrastim	Pegfilgrastim	Cancer, Neutropenia	Sep-13	Lupin
Peg-interferon alfa 2b	Pegylated recombinant human interferon alfa 2b	Chronic hepatitis B, Chronic hepatitis C	Apr-13	Intas Pharmaceuticals
Rasburicase	Rasburicase	Malignancy associated hyperuricemia	Aug-12	Virchow Biotech
Rituximab	Rituximab	Non-Hodgkin's Lymphoma, Rheumatoid arthritis	Feb-15	Reliance Life Sciences
Teriparatide	Teriparatide (parathyroid hormone)	Post-menopausal women with osteoporosis who are at high risk for fracture	Aug-12	Cadila Healthcare
Wosulin	Human insulin	Diabetes mellitus	Aug-03	Wockhardt

CONCLUSION

The recent expiration of patents for some important biologics have given a ray of hope to the biosimilar manufacturers. As these products are proteins, their safety and efficacy will always be considered a concern that should require stringent analysis and pharmacovigilance. Awareness between biosimilar and innovator products in terms of safety, efficacy and immunogenicity is essential for effective prescription and safety of the patients. India the leading producer of biosimilar should frame effective guidelines, nomenclature regulations and proper pharmacovigilance program.

CONFLICT OF INTEREST

There is no conflict of interest between the authors.

ACKNOWLEDGEMENT

The authors are grateful to Sultan-ul-Uloom education Society for providing us the facility to carry out the research work.

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