

Review Article

Biologics and biosimilars: role in modern pharmacotherapy and importance of pharmacovigilance

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ABSTRACT

Biologics are highly sensitive large molecules with complex structure, difficult to characterize and reproduce, derived from living cells; used for treatment, diagnosis or prevention of disease. Examples are therapeutic hormones, vaccines, monoclonal antibodies etc. Biologicals are beneficial in the management of several health conditions which were once upon a time difficult to manage like cancer, multiple sclerosis, Alzheimer's disease, rheumatoid arthritis, diabetes etc. Biosimilars are proteins that are similar to innovator biologics but not the same as they differ slightly in structure however with no clinically significant difference. Biosimilars are not the exact replicas of originator biologic and are therefore not generics. Biosimilars for their approval are not required to undergo intense clinical trials as innovator biologic but are required to produce data that demonstrates its similarity to an original biologic in terms of clinical efficacy and safety. However, manufactures of both the biologics and biosimilars are required to submit pharmacovigilance and risk management plans as part of their application. Marketing authorization for biosimilars was for the first time framed by EMA along with the guidelines for developing them. As biologics and biosimilars are derived proteins they have immunogenic potential and risk of adverse events which cautions their use. Pharmacovigilance is needed to ensure that adverse events are quickly detected, reported and attributed to the correct product and manufacturer. Regulations are implemented to improve identification and traceability of biologics. Automatic substitution should not be permitted for biologicals.

Keywords: Adverse drug reactions, Biologicals, Biologics, Biosimilars, Pharmacovigilance

INTRODUCTION

A new genre of medicine has evolved with the revolution in biotechnology known as Biologicals. Biologicals are large molecules derived using biotechnology for their use in the treatment, diagnosis or prevention of diseases like cancer, diabetes etc. They include proteins such as hormones, vaccines, monoclonal antibodies and many more.¹ Biosimilars though being similar to biologics have naturally occurring minor differences which calls for caution with respect to adverse effects and immunogenicity during their use; signifying the importance of pharmacovigilance. In today's scenario

biologicals are core part of modern armory to manage and treat difficult and rare conditions. They have become an indispensable part of modern pharmacotherapy.²

OVERVIEW

Biotechnology with its advancement gave to the field of medicine a new class of medicines called Biologicals.¹ They are large and complex proteins. They are developed by complex processes making use of living cell lines; as a result of which their reproducibility becomes difficult. Hence, biologics made by one manufacturer cannot be exactly replicated by other manufacturer, and so the term

biosimilars was coined to denote the biologicals that were similar to innovator biologics but not their exact replicas; they had some structural differences compared to innovator biologics but these differences were not clinically significant.³ With the evolution of the biologicals it has been possible to manage several health conditions like cancer, multiple sclerosis, Alzheimer's disease, rheumatoid arthritis, diabetes etc., which were once impossible to manage.² Biosimilars, not having to go through same approval procedures as innovator biologics are comparatively cheaper than biologics; however they are still costlier when compared to generic preparations of chemical drugs.^{3,4} The market of biologic medicines is expected to become \$190-200 billion by the year 2015.⁵ Both biologics and biosimilars being derived proteins have immunogenic potential and risk of adverse events which cautions their use. Therefore, it mandates a strict pharmacovigilance on these products.⁶ In order to aid pharmacovigilance of the biosimilars a unique International Nonproprietary Name (INN) to all the biologics is essential which is facilitated by the naming program that is recommended by the World Health Organization (WHO) and the national regulatory bodies such as the European Commission (EC), UK's Medicines and Healthcare Products Regulatory Agency (MHRA). Such nomenclature would also avoid confusion for the prescribers and the dispensers & also will prevent substitution of biologicals.^{3,8-13}

BIOLOGICALS

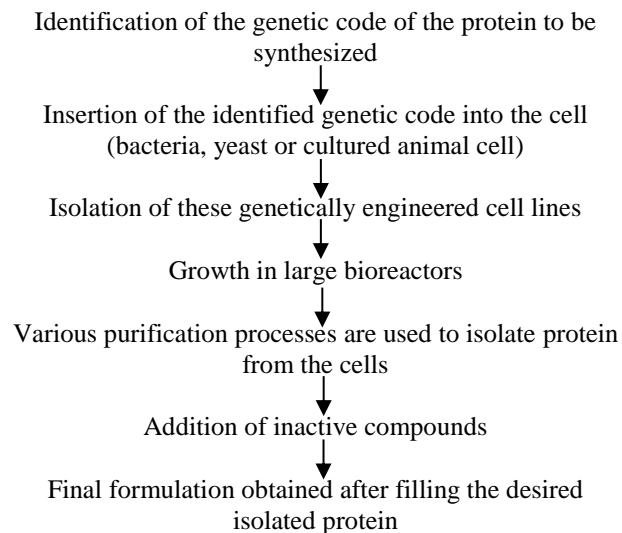
Biologicals are proteins that derived using recombinant DNA technology for their use in the treatment, diagnosis or prevention of various diseases like autoimmune disorders, cancers etc. Unlike chemical drugs that are small in size and can be easily replicated as their chemical structure is known, biologics are large molecules, highly sensitive in nature and their structure being complex and heterogeneous; cannot be easily understood.¹ The characteristics differences between the chemical drugs and biologicals that are highlighted in Table 1.

Table 1: Difference between a chemical & a biological molecule.¹⁴

Chemical drugs	Biologicals
Produced by chemical synthesis	Produced by living cell cultures
Low molecular weight	High molecular weight
Well defined structure	Complex heterogeneous structure
Mostly process independent	Highly process dependent
Completely characterized	Impossible to fully characterize molecular complexity & heterogeneity
Stable	Unstable, sensitive to external conditions
Mostly non-immunogenic	Immunogenic

Manufacturing of biologics

The manufacturing process involves complex procedures requiring recombinant DNA technology which makes its replication difficult.³ The complex procedures include various steps that are described as under:



Every step in the development of biologics is intricate, sensitive and specific to a particular medicine and therefore, even minor alterations lead to changes in cell behavior and differences in the structure, stability or other quality aspects of the end product. Any of these differences that occur will have the potential to affect the treatment's safety, efficacy and shelf life, and to increase the risk of an unwanted immune response.

BIOSIMILARS

Biosimilars as defined by the US FDA are biological products that are highly similar to U. S. licensed reference biological products notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological products and the reference products in terms of safety, purity and potency of the product. They are also known as Subsequent Entry Biologics (SEB) or follow on biologics.¹⁵

BIOSIMILARS VERSUS ORIGINATOR BIOLOGICS

Biosimilars are not exact copies of originator biologic and neither these are expected to be the exact replicas of the innovator biologics as the manufacturing process through which a biologic is made cannot be exactly duplicated by another manufacturer. They are similar to their innovator products but there being some minor difference in the structure due to different manufacturing processes involved they are not the same; however, these differences are not clinically significant and so the clinical outcome with innovator biologics and biosimilars is identical. Albeit both innovator biologics and

biosimilars being protein in nature have immunogenic potential, biosimilars tend to produce more adverse drug reactions than reference products, immunogenicity being the most common among them; as biosimilars do not have to go through the same regulatory approval process as innovator product.^{3,12}

BIOSIMILARS VERSUS GENERICS

Biosimilars are not generics; there is a difference between the two. Generics are exactly identical to their reference products in all the aspects, as the chemical structure of the small (chemical) drugs is completely known and can be exactly duplicated. Whereas the biosimilars are not the exact copies of the innovator biologics as the biologics have complex heterogeneous structure which cannot be exactly replicated and also manufacturing process is complex, a slight change in any of the manufacturing steps produces difference in the products, when the difference is clinically insignificant the manufactured product is termed biosimilar.^{3,8,12,14,16} There are some characteristics differences between generics and biosimilars that are as given in the Table 2.

Table 2: Generics versus biosimilars.

Generics	Biosimilars
Therapeutically equivalent with their reference products (Active product always the same)	Clinically identical to their reference products but not the same (Active product likely to have variation)
Same clinical effect as reference products	Same clinical effect is not seen, there are chances of differences in effects.
Manufacturing simple and consistent	manufacturing complex & variable
Cost of developing is around \$2-3 million.	Cost of developing is around \$75-250 million.
For Approval regulators require bioavailability & bioequivalence studies	For Approval regulators require clinical trials, manufacturing and post-approval safety monitoring programs similar to that of the original innovator companies. They do not accept equivalence
Substitution is permitted for generics	Substitution of biosimilars is not permitted, as the substituted product may not be comparable to prescribed product in terms of safety and efficacy

ROLE OF BIOLOGICALS IN MODERN PHARMACOTHERAPY

They are useful for treatment, diagnosis or prevention of various diseases. They have changed the outlook towards how we treat and manage diseases. Various important

medicines of today are biologicals, including albumin as plasma expander in cases of burns and in cases of liver failure, monoclonal antibodies for cancer, human insulin for diabetes and the cloning of the naturally occurring protein, erythropoietin to stimulate the production of red blood cells in the treatment of chronic anemia are biologics. Many biologicals are being researched all over the world in serious and difficult to manage illnesses. It has been observed that biologicals have made a significant difference to the lives of patients with cancer, blood conditions, auto-immune disorders such as rheumatoid arthritis (RA) & psoriasis, and neurological disorders like multiple sclerosis. It has become possible to target and modify underlying causes of disease, and thus changing the course of disease rather than just treating and managing symptoms in various diseases just like in multiple sclerosis. Biotechnology has given us various management options for cancer treatment, like hormone therapies, biologic medicines and targeted therapies such as monoclonal antibodies.^{1,2} The biologic medicines market is expected to grow to \$190-200 billion by 2015. Although presently the supply exceeds demand, by 2020 the demand is expected to increase over supply.⁵

ISSUES LIKELY TO OCCUR WITH BIOLOGICALS

These include: Quality issues, efficacy issues, safety issues, Pharmacovigilance, Substitution, naming and labeling, Regulatory approval.^{3,8-14,17}

Quality issues, efficacy issues, safety issues

As manufacturing of biologicals is a complex process involving various complicated procedures; every step in the development of a particular medicine is intricate, sensitive and specific. Even minute changes in any of the step lead to changes in cell behavior and thus manifests as differences in the structure, stability or other quality aspects of the end product. Any of these differences have the potential to affect the treatment's safety, efficacy and shelf life, and to increase the risk of an unwanted immune response. Today many companies have started manufacturing biologicals and so regulations are required to ensure that the biologicals manufactured by these companies are safe and efficacious, in order to decrease the morbidity and mortality. Marketing authorization for biosimilars was for the first time framed by EMA along with the guidelines for developing them. This was followed by guidelines from WHO and various other countries.

Significance of pharmacovigilance

Biologics and biosimilars are derived proteins having immunogenic potential and risk of adverse events which cautions their use. Manufactures of both the biologics and biosimilars are required to submit pharmacovigilance and risk management plans as part of their application. Pharmacovigilance is needed to ensure adverse events are

quickly detected, reported and attributed to the correct product and manufacturer.

Regulatory approval of biologicals

Regulators like the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA) require that the innovator companies as well as biosimilar manufacturers submit data to demonstrate a product's efficacy and safety. For approval of innovator biologic the sponsors are required to submit data which includes analysis of structure, functional assays, outcome of animal studies and ultimately the results and interpretations of human trials. Biosimilars for their approval are not required to undergo intense clinical trials as innovator biologic but are required to produce data that shows it to be similar to an original biologic in terms of structure, clinical efficacy and safety. The approval of biosimilar is based on demonstrating similarity of biosimilar to earlier approved reference product. FDA biosimilar guidance (2012) list factors that are to be considered when assessing the similarity of the proposed products to the reference product, which includes; Expression system, Manufacturing process, Physicochemical properties, Functional activities, receptor binding and immunochemical properties, Impurities, Characterization of the reference product and reference standards, Characterization of the finished drug product and Stability. Due to difference in the behavior of biotechnology products and the risks associated with them, manufacturers of both biologic medicines and biosimilars need to submit pharmacovigilance and risk management plans as part of their application.

Naming and labeling

Regulations have also been imposed to improve identification and traceability of biologics. In order to aid pharmacovigilance of the biosimilars an unique International Nonproprietary Name (INN) to the biosimilars is essential which is facilitated by the naming program that is recommended by the WHO and the national regulatory bodies such as the European Commission, UK's Medicines and Healthcare Products Regulatory Agency (MHRA). Such nomenclature would also avoid confusion for the prescribers and the dispensers. Automatic substitution should not be permitted for biologics and biosimilars as it can result in problems like lack of traceability in case of adverse event and confusion in tracing cause of a delayed adverse event.

CONCLUSION

A sudden surge in the biologicals has given a ray of hope in the management of various complicated conditions. Being protein in nature their safety and efficacy is always a concern. Availability of variety of biosimilars for a particular condition possesses the problem of substitution. As a result if adverse event occurs it will not

be possible to track a particular biosimilar. Hence naming, tracking and tracing of biologics plays an important role in case of biologicals. Automatic substitution of the biologics should not be permitted for biologics and biosimilars as it can result in problems like lack of traceability in case of adverse event and confusion in tracing cause of a delayed adverse event. Also in case of adverse event pharmacovigilance is utmost essential which will help us in safe, effective use of biologicals and prevent the occurrence of adverse event. As the market of biologicals is expanding and the biologicals are becoming more and more complex, it is becomes necessary to ensure clarity in prescribing regulations. India being a leading contributor of biosimilars should implement guidelines, nomenclature regulations and strict pharmacovigilance program.

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