EDITORIAL

Biosimilars; Similar But Not The Same

Puneeta Gupta

Pharmaceutical products are doctors' major armamentaria for preventing, curing, controlling or modifying disease processes in order to reduce hospitalisations, disabilities and premature death. These products can be broadly classified into traditional prescription drugs and biopharmaceuticals. The traditional prescription drugs or pharmaceuticals are molecules with a small, well-defined and stable chemical structure that are typically manufactured through chemical synthesis; which means that they are made by combining specific chemical ingredients in a predefined and orderly process by well-controlled and highly reproducible chemical reactions (1).

Unlike single molecules which are chemically synthesised with highly predictable structures and functions, biologics or biopharmaceutical 'biological medicinal products' or 'biological medicines', are medicines which are synthesised or extracted from a biological source often with highly complex structures. These products are polypeptides, (glyco-)proteins, and/ or nucleic acids and their molecular characteristics are much more complex than traditional chemical drug. The manufacturing processes of biologics involve living systems (eg, mammalian cell lines, microbial agents, plants, fungus) and complex processes (eg, gene isolation, recombinant DNA engineering, protein purification); which require high technological expertise with precision in order to ensure consistency and quality of the final product.(2,3)

Increasing knowledge of human diseases, especially after the decoding of the human genome, has accelerated the discovery of disease-related chemicals and/or proteins. These targets form the basis for the design of pharmaceutical compounds to alter biological activities and clinical outcomes. In 1982, the US Food and Drug Administration (FDA) approved human insulin (Humulin) as the first DNA-recombinant protein. Since then, there have been a rapid growth in the number of biologics or biopharmaceuticals in many disease areas, notably oncology, inflammation/autoimmunity and cardiovascular medicine. Major kinds of biopharmaceuticals include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins .(e.g Factor VIII and Factor IX,Thrombolytic agents ,tissue plasminogen activator,hormones insulin, glucagon, growth hormone, gonadotrophins, haematopoietic growth factors ,erythropoietin, colony stimulating factors ,Interferons &Interleukin-based products ,Vaccines,monoclonal antibodies ,and products like ,tumour necrosis factor, therapeutic enzymes etc) (2,3)

There are important differences in the properties of traditional pharmaceuticals and biopharmaceuticals .The final biopharmaceutical product is influenced by many variables, such as the type of expression system, e.g. bacteria, yeast, and mammalian cells; the growth conditions, the purification process, the actual formulation and the conditions during storage and transport. Post-translational modifications occur during cellular synthesis, such as glycosylation, phosphorylation, sulphation, methylation, acetylation and hydroxylation which may affect biological activity and which results in an intrinsic molecular heterogeneity. It can be calculated, theoretically, that these modifications may result in more than one million product-related variants. Since this structural variability is substantial and can be very subtle, the currently available analytical techniques are insufficient to fully characterise the end product.

Thus in contrast to traditional prescription drug which can be analyzed to determine all its various components, it is difficult or even impossible to break down the components of a complex biologic. In fact, some of the components of a finished biologic may be unknown . While a traditional drug manufacturer can change the manufacturing process extensively to produce an identical final product, the living cells used to produce biologics can be sensitive to very minor changes in the complex manufacturing process. Small differences in the process can significantly affect the nature of the finished biologic drug and the way it works in the body. Importantly, and in contrast to traditional chemical drugs, biopharmaceuticals are potentially immunogenic.

Starting with insulin three decades ago, biologics have become the fastest-growing class of therapeutic compounds. About 300 biologics are now available for human use. These compounds are widely accepted as the most effective means of treating certain diseases, including cancer and rheumatoid arthritis. Gene-based

From the Department of Medicine ASCOMS, Sidra, Jammu J&K- India 1800001
Correspondence to : Dr Puneeeta Gupta, Professor Deptt. of Medicine , ASCOMS, Sidra, Jammu (J&K) -India 180001

Table.1 Following table shows important differences between generics and biosimilars ;

Properties	Generics	Biosimilars
Size	Small	Large
Molecular Weight	~ 150 Daltons	~150,000 Daltons
Structure	Simple And Well-Defined	Complex
Manufacturing	Predictable Chemical Process	Specialized Biological Process
Complexity	Easy To Fully Characterize	Difficult To Characterize
Stability	Relatively Stable	Sensitive To Storage And Handling
Immune Reaction	Lower Potential	Higher Potential
Quality Tests	= 50	= 250
Approval Requirements	Clinical Trials-Healthy Volunteers	Large Clinical Trials-Patients

and cellular biologicals, for example, often are at the forefront of biomedical research, and may be used to treat a variety of medical conditions for which no other treatments are available ; thus bringing hope to those with few other alternatives. Indeed, the demand for biologics is growing exponentially due to their ability to bind to specific cells, which means they have fewer side effects than broadly acting drugs .Data from United States revealed that w hile only 1 percent to 2 percent of the population in the country is treated with a biologic each year, these drugs accounted for 38 percent of prescription drug spending in 2015. In addition, biologics accounted for 70 percent of the growth in prescription drug spending in the U.S. between 2010 and 2015, practically accounting for 50% of hospitals' pharmaceutical spending, . In 2016, more than 10 biologics were blockbuster drugs with annual revenue of billions of dollars.(4) .Sales of biologics are expected to exceed AUS$300 billion annually by 2019. (4,5)

What is a biosimilar

The biosimilar has been defined as a biological product that is highly similar to a licensed reference biological product notwithstanding minor differences in clinically inactive components, so that there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product (6)

Because of their intrinsic complexity and because no two cell lines, developed independently, can be considered identical, biopharmaceuticals cannot be fully copied.. This is recognised by the regulatory authorities and has resulted in the establishment of the term 'biosimilar' in recognition of the fact that, whilst biosimilar products are similar to the original product, they are not exactly the same . When a "biosimilar" is created it requires a new manufacturing process, beginning with new starting materials, resulting in a product that is different from and not therapeutically equivalent with that of the brand name biologic. (6.7) Because of the complex process of manufacturing biologics, the only way to establish whether there are differences that affect the safety and effectiveness of the biosimilars is to conduct clinical trials on each new product .Thus a biosimilar, sometimes called 'similar biological medicinal product' or 'follow-on biologic' or 'subsequent entry biologic' , is a medicine that is similar to a biopharmaceutical that has already been authorised (the 'reference product') (6.7.8).

Generics and biosimilars ; what is the difference: When a pharmaceutical company introduces a costly new drug, they can do so because they have an exclusive patent on it. Once drug patents expire, other pharmaceutical companies can copy that branded drug, and sell it for significantly less as a generic .A generic drug is the same as a brand name drug in dosage, safety, strength, quality, performance, and intended use. By law, a generic drug product must contain the identical amounts of the same active ingredient(s) as the brand name product. With the make-up of the drug already approved, generics do not require the added expenditure of research and development , thus the final cost to the manufacturer and the consumer is much lower because the approval pathway is much shorter than branded drugs. On the other hand, both biosimilars and their reference drugs are not synthesised through a simple chemical reaction like generic drugs. They require a complex biotechnological process in a cellular environment like other protein from the body. Strictly speaking, there's no such thing as a generic biologic because the term "generic" only applies to small-molecule drugs made by traditional chemical processes. In generic medications, the active ingredients are identical molecules to the brand name drug, but this can't be the case when a living cell produces the drug. (9)

Since the active substance of a biosimilar is similar but not identical to the active substance of the reference product the regulatory requirements for approval of generics are inadequate to demonstrate the quality, efficacy, and safety of biosimilars. In Europe and North America, regulatory agencies such as the European Medicines Association and FDA have developed clear regulatory guidelines for the evaluation and approval processes of biosimilars regarding their physical, chemical and clinical traits.Thus, given their complexity, biosimilars may require an investment of around 3 to 4 billion dollars

as against a few million dollars in case of generic drugs. Furthermore, while a generic drug can reach the market within an estimated period of 2 to 3 years, a biosimilar drug needs between 7 and 8 years in order to be marketed. All this time needed to develop biosimilars is due to the numerous studies necessary for their authorisation, including pharmacokinetic studies.(10,11).

With ageing and modernisation, non-communicable diseases (NCD) such as cancer, diabetes, chronic kidney disease and inflammatory diseases are now the leading causes of death worldwide. Thus, after long disease duration, patients with type 2 diabetes may require insulin analogues with different formulations (long acting, short acting, ultra-short acting, ultra-long acting) to control their diabetes. Some of these patients may go on to develop renal failure and require erythropoietin for treatment of anaemia. Given the close links between diabetes and cancer.(12) some of these patients may receive biologics/ biosimilars for cancer treatment and drug-induced neutropaenia. On the other hand, anticancer therapies for hormone-sensitive cancers or pancreatectomy for pancreatic cancer may lead to diabetes resulting in complex therapies. Similarly, there are close links among chronic inflammatory diseases, autoimmunity and cancer (eg, type 1 diabetes, ulcerative colitis, Crohn's disease, systematic lupus erythematosus, rheumatoid arthritis) that can further increase the complexity of their biologics treatment.(13)

The availability of biosimilars will have an impact on drug costs. For example , in United States, introducing "biosimilar" versions of complex biologic drugs used to treat illnesses such as cancer and rheumatoid arthritis could cut health care spending by $54 billion over the next decade. This impact will not be as dramatic as that of generic small-molecule drugs, because manufacturing biosimilars is much more difficult. The expectation is that the price will decline by approximately one-third, or possibly by as much as one-half. With generics, by contrast, the cost often is reduced by 90% to 95%, or even more. The patents are expected to expire for for some of important biological like adalimumab, insulin glargine, etanercept, infliximab, rituximab, pegylated filgrastim, trastuzumab and follitropin alfa, amongst others; drugs which currently produce 42.3 billion euros in sales in Europe and the United States.

Thus, with increasing number of biologics coming off patents, more patients are expected to benefit from these therapies even in low-income to middle-income countries where prevalence and incidence of NCDs are rising rapidly. (14) .

References

1. Neumann PJ, Sandberg EA, Bell CM, *et al*. Are pharmaceuticals cost-effective? A review of the evidence. *Health Aff* 2000;19:92-109.
2. Juliana CN, Chan, Anthony TC, Chan. Biologics and biosimilars: what, why and how? *ESMO Open* 2017; 2(1): e000180.
3. Kinch MS. An overview of FDA-approved biologics medicines. *Drug Discov Today* 2015;20:393-98.
4. Andes S, Bockello M, Larson C, *et al*. Trends in Biosimilars Report. *Amgen* 2015
5. Ebbers HC, Chamberlain P. Controversies in establishing biosimilarity: extrapolation of indications and global labeling practices. *BioDrugs* 2016;30:1-8.
6. Camacho LH, Frost CP, Abella E, *et al*. Biosimilars 101: considerations for U.S. oncologists in clinical practice. *Cancer Medicine* 2014;3:889-99.
7. US Department of Health and Human Services. Scientific considerations in demonstrating biosimilarity to a reference product. Guidance for industry. Available at : http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm291128.pdf. Cited On: Jan, 2017
8. Kozlowski S. US FDA Perspectives on Biosimilar Biological Products. Presented at: 2014 Biotechnology Technology Summit; June 13, 2014; Rockville.
9. Godman B. Health authority perspective on biosimilars. *Generics and Biosimilars Initiative J* 2013;2:10-11.
10. Mullard A. Hearing shines spotlight on biosimilar controversies. *Nat Rev Drug Discov* 2010;9:905-6.
11. Roger SD. Biosimilars: how similar or dissimilar are they? *Nephrology* 2006;11:341- 6.
12. Giovannucci E, Harlan DM, Archer MC, *et al*. Diabetes and Cancer: a consensus report. *Diabetes Care* 2010;33:1674-85.
13. Franks AL, Slansky JE. Multiple associations between a broad spectrum of autoimmune diseases, chronic inflammatory diseases and Cancer. *Anticancer Res* 2012;32:1119-36
14. Lozano R, Naghavi M, Foreman K, *et al*. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the global burden of disease study 2010. *Lancet* 2012;380:2095-128.