

From biologicals to biosimilars

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Biopharmaceuticals are a cornerstone of therapy for a wide spectrum of diseases, from cancer to autoimmune or autoinflammatory diseases.¹ Biologicals (biologics) are very effective but expensive, hence not prescribed commonly in developing countries. To counter this problem many biosimilar products are under development as the patents for various biologicals are expiring. Differences between biologicals, biosimilars, interchangeable products and generics should be understood.

Biologics are genetically engineered proteins derived from human genes. They are designed to inhibit specific components of the immune system that play pivotal roles in fueling inflammation. Biologics are composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues.¹ Biologics are isolated from a variety of natural sources - human, animal, or microorganism - and may be produced by biotechnology methods and other cutting-edge technologies.¹

US FDA defines biosimilar as the biological product that is highly similar to a U.S. licensed reference biological product not withstanding minor differences in clinically inactive components, and for which 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.²

World Health organization defines it as a biotherapeutic product that is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product.³

According to European Medicines Agency it is a biological medicine that is developed to be similar to an existing biological medicine. When approved a biosimilar's variability and any differences between it and its reference medicine will have been shown not to affect safety or effectiveness.⁴

Biosimilars have been shown to have no clinically meaningful difference from the reference product whereas an interchangeable biological product is similar in composition as well as is expected to produce the same clinical result as the reference product in all the patients.¹

Generics or follow-on compounds are composed of small molecules, which are identical copies of active substances produced by chemical synthetic method. In contrast, identical copies of biologics cannot be produced as they are 10-1000 times larger than a small molecule drug and have a complex three-dimensional structure.¹

To support consistent analyses across geographies, therapies, and manufacturers, IMS Health has established an industry-verified categorization of biologics. Although not every

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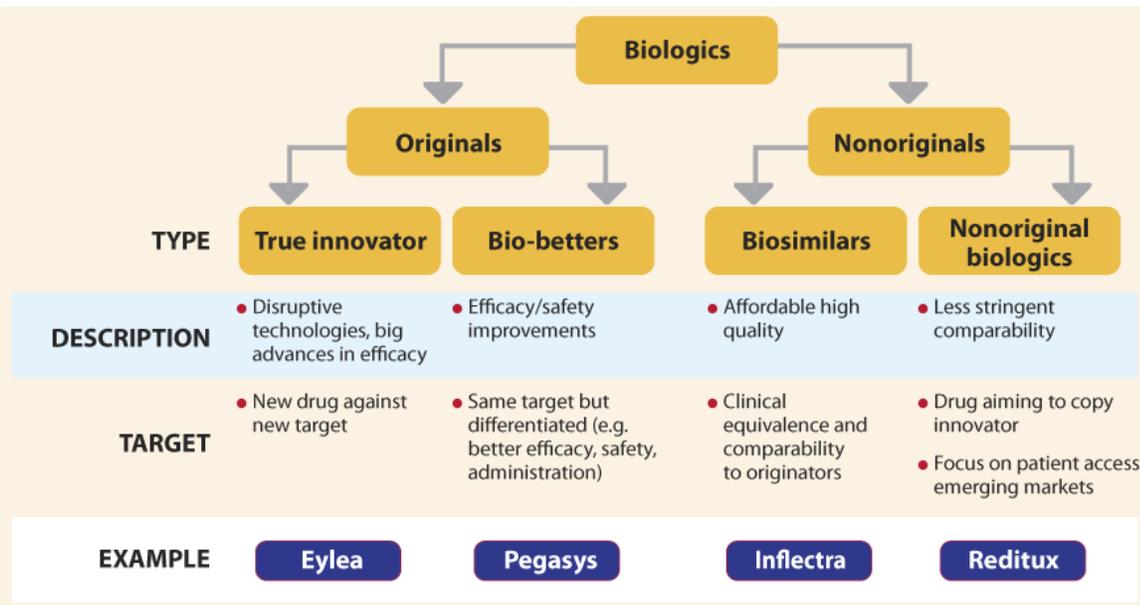


Figure 1 Classification of biologics [5].

product fits neatly into these classifications, the schema applies in most instances (Figure 1).⁵

Biologics and biosimilars are produced in living cells including humans, animals and microorganisms such as bacteria or yeast. They are manufactured through cutting-edge biotechnology in a multistep process. At the beginning a basic protein structure is translated from a DNA sequence followed by changes in the structure of basic protein called posttranslational modifications.^{5,6} After formulation of basic protein its quality control, purification and production of end product requires some strict parameters including control of temperature, pH, agitation and types of containers used. The modifications in manufacturing of biosimilar may cause different types of changes, which can affect the quality, safety or efficacy of the product.^{7,8}

In Europe first biosimilar was approved in 2006 and uptill now 16 biosimilars have been approved from three categories including human growth factor (G-CSF), erythropoietin and a monoclonal antibody. Valtropin is a biosimilar of Humatrope (somatropin, human growth

hormone), Inflectra and Remsima for infliximab and Filgrastim for Neupogen (human granulocyte-colony stimulating factor).¹ Rituximab and trastuzumab biosimilars are also under development.¹

Biological therapies pose a significant economic burden to health care systems. The development of biosimilars will prove to be cost-effective with broader access to the patients especially in third world countries. Nevertheless, certain issues need to be addressed. Although biosimilars are similar in structure to their originals, there are subtle differences, which may affect the efficacy and safety of biosimilars. So, before getting approval of the regulatory agencies, a biosimilar should be subjected to adequately powered clinical trials with well-defined efficacy and safety endpoints. Secondly, being proteins, biosimilars can induce antiproduct antibody formation thus jeopardizing their clinical efficacy. A well-designed postmarketing monitoring will be required to document rare and severe adverse events when this class of drugs is widely used in patients.

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