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Biologics with a greater reach

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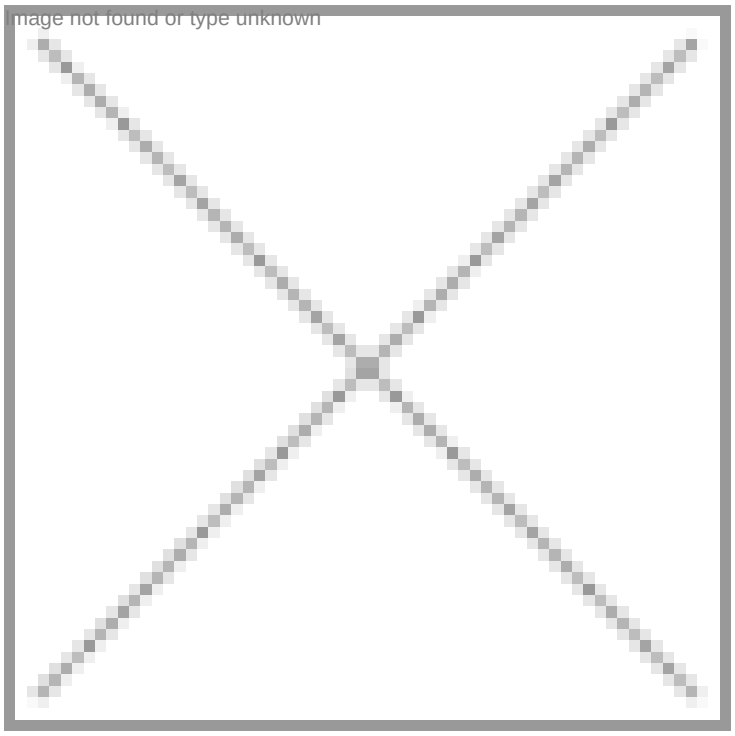

Biologics with a greater reach

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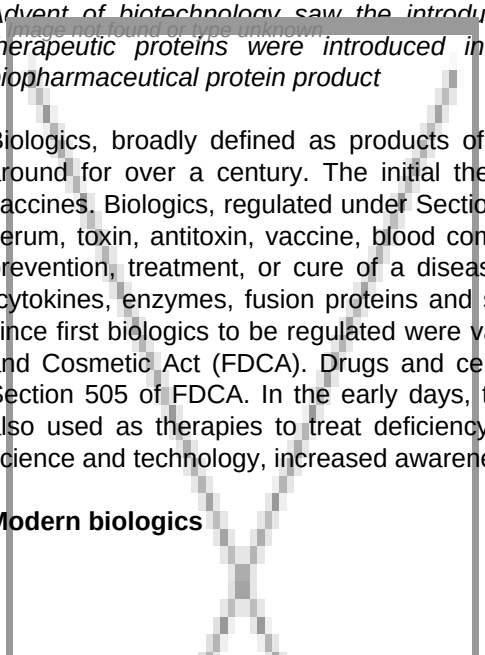


Biologics, broadly defined as products of living organisms for diagnosis, prevention or treatment of disease, have been around for over a century. The initial therapies ranged from anti-toxins (e.g. diphtheria and tetanus) to heat-inactivated vaccines. Biologics, regulated under Section 351 of the Public Health Service Act (PHSA) are defined as “a virus, therapeutic serum, toxin, antitoxin, vaccine, blood component or derivative, allergenic product, or analogous product, applicable to the prevention, treatment, or cure of a disease or condition of human beings.” Analogous products include: protein products (cytokines, enzymes, fusion proteins and some hormones), monoclonal antibodies, and gene therapy products. In the US, since first biologics to be regulated were vaccines, they are licensed (via biologic licenses) under PHSA and not Food, Drug and Cosmetic Act (FDCA). Drugs and certain simpler biologics such as insulin and growth hormone are approved under Section 505 of FDCA. In the early days, therapeutic proteins purified from natural sources, including animal tissues, were also used as therapies to treat deficiency disorders (e.g. insulin deficiency and growth hormone deficiency). Progress in science and technology, increased awareness, and better regulatory systems led to the availability of improved biologics.

Modern biologics

The advent of biotechnology saw the introduction of recombinant biologics, where the DNA sequences coding for specific therapeutic proteins were introduced into bacterial, yeast or mammalian cells which multiplied and produced the biopharmaceutical protein product. They could be loosely viewed as second generation or follow-on products of therapeutic proteins that were earlier being purified from natural sources. The first recombinant therapeutic product was Eli Lilly's insulin, Humulin, approved in 1982. More than 250 biotechnology derived medicines have been licensed for use in humans, and many more are in preclinical and clinical development. These include, simple peptides and proteins as well as more complex therapies like monoclonal antibodies, fusion proteins and cell based therapies.

Biopharmaceutical products versus small molecule drugs

Biologics or biopharmaceutical drugs are large, complex molecules, produced in living cells. When compared to conventional small molecule chemical drugs, even simple proteins are 100 to 1,000-fold larger and more complex. Some of the more complex proteins and monoclonal antibodies undergo post-translational modifications resulting in the addition of carbohydrates or lipids to the protein component, contributing to heterogeneity and differences in immunogenicity. The molecules can also adopt different secondary and tertiary structures beyond their primary amino acid sequence.

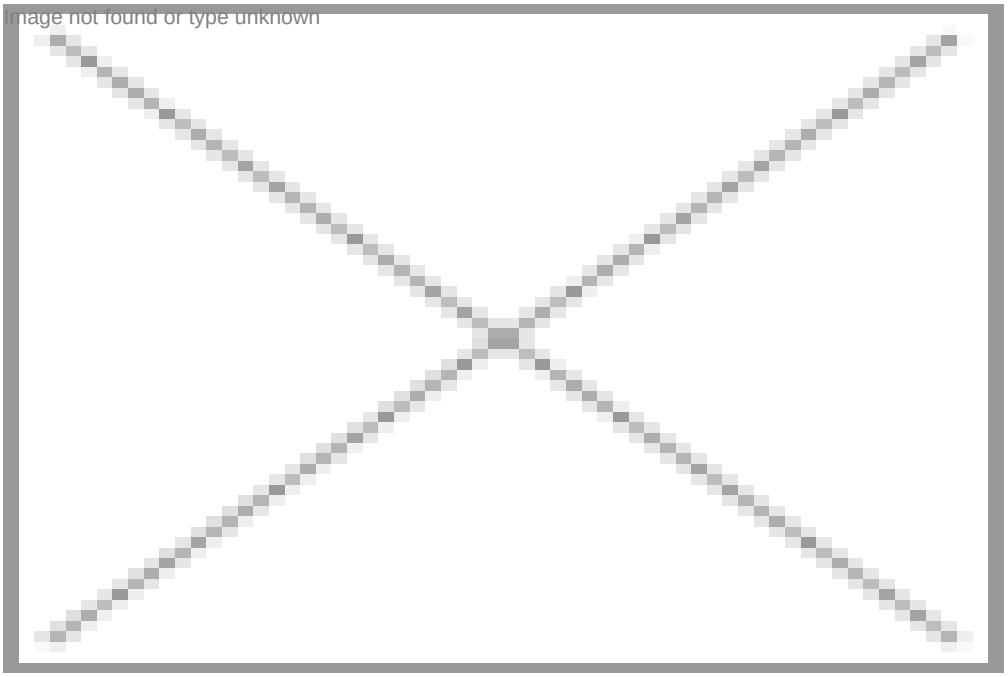
The methods of production of biologics are more capital-intensive and complex, and the products are more difficult to characterize, resulting in increased costs in bringing the product to the market. This is partly the reason why biologic medicines are in general much more expensive than chemical drugs. One estimate puts the average cost of a biologic drug treatment at $72,000/year (Rs 33.94 lakh) when compared to approx. $1,000/year (Rs 47,150) for a chemical drug. Global sales of biologics in 2008 was $120 billion (Rs 5.65 lakh crore), of which monoclonal antibodies contributed $33 billion (Rs 1.55 lakh crore), vaccines $24 billion (Rs 1.13 lakh crore), TNF blockers $18 billion (Rs 84,860 crore), insulins (including newer inhaled insulin) $12.5 billion (Rs 58,900 crore), erythropoietins for anemia $9.5 billion (Rs 44,790 crore)and interferons $8 billion (Rs 37,700 crore).

Biosimilars and follow-on biologics

The high costs of biologics and patent expiry of some of the older recombinant protein molecules created opportunity for companies to produce copy-cat versions of the molecules. Unlike for small molecule drugs, a regulatory framework for the introduction of generic versions of a biologic after patent expiry did not exist until recently. Biologics are produced by a complex process involving living cells, e.g. E. coli, yeast or mammalian cells. The specific clones or strains that are used to produce the innovator's molecule are proprietary and not available for others. Therefore, it is nearly impossible that one will be able to produce and prove that generic copies of the innovator's molecule are identical to the reference molecule, even with extensive analytical and pre-clinical evaluation. Therefore, the European Medicines Agency (EMEA) has used the term 'biosimilars' (similar biological medicinal products) instead of biogenerics to describe them, and adopted a new directive to pave way for legal approval of biosimilars in EU in 2004. In the US, the term follow-on biologics (FOB) or follow-on protein product (FOPP) is being used but it may be some time before a regulatory path for their license/approval is established. Even in Europe, biosimilars are being evaluated on a case-by-case basis since different classes of molecules may require specific guidelines for establishing comparability/similarity in quality, efficacy and safety. Some of the biosimilar medicines that have been approved for use in Europe are listed in the table on page 25.

In 2006, Omnitrope was found to be structurally identical to Pfizer's Genotropin and it was approved through 505(b)(2) pathway as a new drug application under Hatch-Waxman Act. Though Omnitrope is available in the US market, it is not rated

AB like most generics and is not technically a biosimilar.



Are all biosimilars truly similar?

Human growth hormone and insulin are much simpler molecules and are much easier to test when compared to more complex molecules like erythropoietin and monoclonal antibodies. Monoclonal antibodies are more complex and have multiple domains that may play a critical role in clinical activity of the molecule. Additionally, one monoclonal antibody may be indicated in multiple diseases. Different combination of multiple activities may be required for being efficacious in each indication. Variation in glycosylation and immunogenicity are also major concerns with regard to establishing comparability of monoclonal antibodies. There have been debates in the recent years over how much clinical testing is required for a biosimilar, and how much and to what extent clinical data is necessary for marketing approval. Most regulators and innovator companies maintain that zero-tolerance to patient safety should be the standard approach. They contend that it is impossible to truly evaluate the immunogenicity or potential for adverse events in proteins without using proven clinical methods. One could also argue that with the progress in science and technology, it should be possible to develop better processes and better products than the existing innovator's patented process. Therefore, it is also possible that all biosimilar molecules may not prove to be as good as or better than the innovator's molecule. Careful evaluation of each molecule with regard to its comparability, safety and efficacy will be needed. For instance, EPO from Sandoz has received the same INN (international non-proprietary name) as that of the original Epogen from Amgen (EPO-alpha) while Stada's biosimilar EPO received the INN of EPO-zeta and is not interchangeable with Epogen.

Biosimilars are here

Since biologic drugs are often used to treat life-threatening diseases, and are unaffordable to the vast majority of people in the world, the availability of good quality biosimilars at an affordable cost is a boon to many. Companies in India, China, South Korea and Europe have grabbed the opportunity and brought biosimilars to the market at cheaper prices. Health Canada maintains that no true biogenerics exist and uses the term subsequent entry biologics (SEBs) to refer to biosimilars. Canada and Japan are still working on a comprehensive regulatory framework for SEBs or biosimilars, and the US may not be far behind.

A great opportunity is likely just around the corner for Indian biopharmaceutical companies that can keep the cost of development down while maintaining or improving the quality of their biosimilar products.