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Biopharmaceuticals: A Review of Biopolymeric Drugs and Accessibility Challenges in India

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Abstract

Advances in biotechnology have allowed us to produce biosynthesized proteins that have therapeutic benefits. The drug products having biotechnology derived proteins, i.e. Biopharmaceuticals, have evolved the treatment of several diseases. knowledge about biological systems have been explored scientifically, there have been significant efforts to utilize them for improving human lives. These biopharmaceutical products have a rapidly growing market which needs to be closely monitored to avoid any potential risks. This review emphasizes on the scenario of the biopharmaceutical products available in India and some important aspects to be considered to facilitate their safe use. Biologics are defined by the Central Drug Control Organization (CDSCO) as 'drugs derived from any natural source (microorganism, animal or human).' Indian Pharmacopoeia Commission (IPC) Biologics are comprised of proteins, sugars, nucleic acids, or a blend of these components, and may also encompass living organisms like cells and tissues. Since the biotechnological methods used to obtain these biologics are not economical, this makes these products extremely unaffordable to the majority of the population in developing nations. Continued investments in research, infrastructure, and talent development will be essential to harness the full potential of polymeric biopharmaceuticals and address unmet medical needs in India and beyond.

Keywords: Biopharmaceutical, Therapeutic Benefits, Biologics, Indian Pharmacopoeia, Genetic Engineering, Polymer.

INTRODUCTION

Ever since the knowledge about biological systems have been explored scientifically, there have been significant efforts to utilize them for improving human lives. Biotechnology today utilizes living organisms, influences biological processes in order to generate products intended for human use. The products with applications in therapeutics or disease management are commonly referred to as biotechnological products, more commonly called *biologics*. [1,2]

The active components in these products are most commonly biotechnologically derived proteins, consisting of several amino acids. These therapeutic proteins are used as active agents and formulated suitably into drug products called *biopharmaceuticals*. Till date biopharmaceuticals have been proven useful in cancer, auto-immune disorders, osteoporosis, macular degeneration and several infectious diseases. [3, 4]

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nucleic acids, or a blend of these components, and may also encompass living organisms like cells and tissues. Biologicals can be produced from various natural sources as well as through rDNA (recombinant DNA) based technology.' [5, 6]

Since the biotechnological methods used to obtain these biologics are not economical, this makes these products extremely unaffordable to the majority of the population in the developing nations. Most of the biologics are protected under Intellectual Property Rights, but as the patent expires other companies interested can manufacture a similar biologic, known as *Biosimilar*. [7, 8, 9, 10] Biosimilars are biological products, known as originally approved products, that have the same security and clinical effectiveness as the original approved product. However, biosimilars cannot be asserted as identical to the reference product due to the intricate structure of proteins, often mixture of isoforms, nature of manufacturing process, post-translational modifications, instability due to higher sensitivity to physical conditions, etc. [11, 12, 13, 14]

GUIDELINES AND REGULATIONS

The world market for biosimilars is growing, and so is the demand for affordable biosimilars, particularly in developing countries like India. CDSCO, the national regulatory authority in India, is accountable for monitoring the security, effectiveness, and excellence assessment of medications in the country. The Department of Biotechnology (DBT) oversees the advancement and clinical assessment of various hybrid DNA (rDNA) products through the Review Committee on Genetic Manipulation (RCGM). CDSCO and DBT collaborated to publish 'Similar Biologics guidelines' in 2012, subsequently revised in 2016. These guidelines outline the regulatory pathways associated with the manufacturing process, safety, efficacy, quality, pre-clinical and clinical studies aspects for biosimilars. [15]

In October 2015, a separate "Division of Biology" was established at IPC to develop biological monographs and standards in the Indian Pharmacopoeia: [7]

- Human vaccines and immunosera
- Blood and blood-related products
- Allergen products
- Therapeutic products derived from biotechnology.

The 'Similar Biologics Guidelines' revised in 2016 had a significant impact on the biopharmaceutical landscape in India. These guidelines, also known as the "Guidelines on Similar Biologics: Regulatory Requirements for Marketing Authorization in India," were introduced by the Central Drugs Standard Control Organization (CDSCO), the regulatory body responsible for approval of drugs and medical devices in India. Here's a detailed analysis of their impact:

1. **Expansion of Biologics Market:** The revised guidelines provided a clear regulatory pathway for the approval of similar biologics, also known as biosimilars or follow-on biologics, in India. This encouraged more companies to invest in the development of biosimilars, leading to an expansion of the biological market in the country. This expansion has been particularly significant in areas such as oncology, diabetes, and autoimmune diseases.
2. **Increased Competition:** With more companies entering the biosimilars market, competition has intensified. This has led to greater affordability and accessibility of biologic therapies for patients in India. Increased competition has also encouraged innovation and the development of more advanced biologics.
3. **Boost to Biotech Industry:** The introduction of clear regulatory guidelines has provided a boost to India's biotechnology industry. Domestic biotech companies have been able to leverage their expertise in biologics development to enter the biosimilars market. Additionally, multinational pharmaceutical companies have also invested in establishing biologics manufacturing facilities in India to cater to both domestic and international markets.
4. **Enhanced Regulatory Standards:** The revised guidelines have helped in strengthening regulatory standards for the approval of biosimilars in India. This has increased confidence among

healthcare professionals and patients regarding the safety, efficacy, and quality of biosimilar products available in the market.

5. **Challenges and Concerns:** Despite the positive impact, there are some challenges and concerns associated with the implementation of the guidelines. One major concern is the need for robust pharmacovigilance systems to monitor the safety of biosimilars post-market approval. Additionally, there may be challenges related to the interchangeability and substitution of biosimilars, as well as concerns regarding immunogenicity and variability between batches.
6. **Global Recognition:** India's regulatory framework for biosimilars has gained recognition globally. The revised guidelines have brought India in line with international standards, facilitating the export of biosimilar products to various global markets. Indian biopharmaceutical companies have increasingly been able to compete on a global scale, contributing to the country's reputation as a hub for high-quality and affordable biologics.

Overall, the 'Similar Biologics Guidelines' revised in 2016 have had a transformative impact on the biopharmaceutical landscape in India, driving innovation, competition, and accessibility in the biosimilars market while also raising regulatory standards and fostering growth in the biotech industry.

CURRENT SCENARIO IN INDIA

The Genetic Engineering Appraisal Committee (GEAC) functions under the Ministry of Environment, Forest, and Climate Change (MoEF&CC). Established by the 1989 Regulation, it is tasked with assessing activities involving the utilization of hazardous and recombinant microorganisms in research and production from an environmental standpoint. [16]

Several companies in India have manufactured a variety of biopharmaceutical products including vaccines, monoclonal antibodies, insulin and recombinant proteins. “Reddy Laboratories, Ranbaxy, Biocon, Reliance Life Science, Panacea Biotech, Bharat Biotech etc. It also sells a number of certified blood products, like some Indian companies”: [17, 18, 19]

- Coagulation factors- Human Prothrombin, Human Plasma coagulation factor VII, IX, Fibrin sealant, etc.
- Human Albumin solution IP
- Immunoglobulins- Human anti-D immunoglobulin, Hepatitis B immunoglobulin, Human Tetanus immunoglobulin etc.
- Fresh frozen plasma

FUTURE PERSPECTIVES

A biosimilar differs from its innovator biologic and is not identical to it, unlike a generic API is identical (chemically & therapeutically) to its original branded alternative. Unlike the precisely structured low molecular chemical drugs which are easy to reproduce on a large scale, macro molecular biopharmaceuticals possess intricacy in three 3-D fragile framework which are not easy to accurately duplicate. Different manufacturers may use distinct cell lines, protein sources, extraction and refinement techniques compared to what was used in the innovator product, and additionally even slight physical changes during the manufacturing processes may ultimately increases the heterogeneity of the biopharmaceutical. [20, 21, 22, 23]

The two most concerning aspects that need to be addressed related to the use of biosimilars are their varying efficacy & immunogenicity. A study in past compared 11 different epoetin alfa products from Argentina, China, India and Korea revealed a significant variation in *in-vivo* bioactivity, ranging from 71-226%. Immunogenicity is the potential of a therapeutic protein to stimulate antibody reaction. An example of such unwanted immunogenicity is that Pure red cell aplasia occurs in patients treated with Eprex (biosimilar of epoeitin alfa). The most likely cause was the slight manufacturing deviation by using Polysorbate 80 instead of the human albumin stabilizer in the formulation. Another instance

involves the withdrawal of Peginesatide (Omontys), a PEGylated peptide product, from the market in 2013 due to post-marketing reports of hypersensitivity reactions". [24, 25, 26, 27]

The world as well as India is evolving rapidly in the production and use of biosimilars. India has a great potential to be a global player in the biopharmaceutical industry which is shown in Table 1. This growing demand for manufacturing of biologics is driving innovations to simplify the complex biosynthesis of biologics, one such technique in dawning is known as Cell free Production System (CFPS). CFPS is a manufacturing process involving small scale production of biologics without the need to use a living cell, as cell viability often limits the desired protein yields. [3, 28, 29, 30]

Table 1. List of New Drugs (Recombinant DNA Origin) Approved for Manufacturing and Marketing in India by CDSCO in 2023 [31]

S.N.	rDNA product	Therapeutic indication	Firm name	Date of Permission
1	Cetuximab	Head and neck tumors.	M/s Enzene Biosciences Ltd.	16-01-2023
2	Tenecteplase	Tenecteplase is prescribed for the thrombolytic treatment of suspected myocardial infarction with sustained ST increasement in adults or within 6 hours of the onset of symptoms of acute myocardial infarction (AMI).	M/s. Hetero Biopharma Limited	31-01-2023
3	Erythropoietin	Bleeding is linked with chronic renal failure in adults undergoing peritoneal dialysis or hemodialysis, as well as in non-dialysis adults.	M/s Wockhardt Limited	14-02-2023
4	Bevacizumab	Individuals diagnosed with metastatic carcinoma of the colon or rectum receive treatment in conjunction with fluoropyrimidine-based chemotherapy.	M/s Enzene Biosciences Ltd.	21-02-2023
5	Ranibizumab	It is prescribed to treat neovascular age-related macular degeneration (AMD).	M/s Sun Pharmaceutical Industries Ltd.	24-03-2023
6	Denosumab injection	• Treatment for increasing bone density in men diagnosed with osteoporosis at a heightened risk of fracture.. • Managing bone loss linked with long-term systemic glucocorticoid therapy in patients at high fracture risk. • Managing bone density enhancement in men with a high risk of fractures undergoing androgen deprivation therapy for unresectable prostate cancer. • Managing bone density enhancement in women with a high risk of fractures undergoing adjuvant aromatase inhibitor therapy for breast cancer.	M/s Enzene Biosciences Ltd.	10-04-2023
7	Golimumab Injection	Golimumab, when used alongside methotrexate (MTX), is prescribed to treat older individuals with moderate to intense rheumatoid arthritis.	M/s Reliance Life Sciences Pvt. Ltd.	26-04-2023
8	Ustekinumab	Ustekinumab is prescribed to treat older individuals with moderate to intense plaque psoriasis.	M/s Reliance Life Sciences Pvt. Ltd.	26-04-2023
9	Ustekinumab Drug Substance (Bulk)	NA	M/s Reliance Life Sciences Pvt. Ltd	16-05-2023
10	Golimumab Drug Substance (Bulk)	NA	M/s Reliance Life Sciences Pvt. Ltd	16-05-2023
11	Adalimumab	• Adalimumab is prescribed for Rheumatoid Arthritis (RA) in adults. • Moderate to intense, energetic rheumatoid arthritis (RA). • Intense, energetic, and incremental RA	M/s Shilpa Biologicals Private Ltd.	22-06-2023

12	Adalimumab Drug Substance (Bulk)	NA	M/s Shilpa Biologicals Private Ltd.	24-08-2023
13	Ranibizumab Injection	Neovascular Age-Related Macular Degeneration	M/s Enzene Biosciences Ltd.	29-08-2023
14	Liraglutide	It is prescribed for the treatment of neovascular age-related macular degeneration.	M/s Levim Biotech LLP	24-08-2023
15	Ranibizumab	It is prescribed for the treatment of neovascular age-related macular degeneration. (AMD).	M/s Zenotech Laboratories Limited	05-10-2023
16	Tenecteplase	Tenecteplase (TNK-t-PA) is suggested in thrombolytic treatment of the Acute Ischemic Stroke within 4.5 hrs of the stroke initiation	M/s Gennova Biopharmaceuticals Ltd	27-10-2023

Source: *CDSCO, Government of India.*

FORMULATION DEVELOPMENT ASPECTS

Since the active molecules present in biopharmaceuticals are essentially macromolecular proteins, they are susceptible to various enzymes and alterations in pH values in the gut. Only a limited number of orally administered products, such as poliomyelitis and salmonella vaccines, are infectious via the oral route. A recent development is glucagon-like peptide-1 (GLP-1), an oral formulation of semaglutide. formulated using an absorption enhancer, as an alternative to Insulin injectables. Another promising delivery system is micro-needles via the dermal route. [32, 33, 34]

The pulmonary route is another alternative, e.g. Pulmozyme (Dornase alfa) is a biologic administered by inhalation which is administered in Cystic fibrosis patients to break down DNA in sputum. Intravenous administration of the vascular endothelial growth factor (VEGF)-binding mAb biologic Lucentis (Ranibizumab) has also been approved for addressing age-related macular degeneration treatment. [35, 36]

STABILITY AND STORAGE

The handling of biologics is a crucial step because due to the intricate tertiary structure of active protein molecules which are sensitive to even slight alterations in various physical conditions. The storage conditions mentioned by the manufacturers must be strictly obliged to, avoiding heat shock while transporting, shaking the product for preparing injection. Inappropriate handling may result in protein aggregate formation thereby increasing immunogenicity. Additionally, mishandling may contribute to compromise in container integrity, resulting adversely on the product sterility. [37, 38]

DISCUSSION

Biosimilars and original biopharmaceuticals, though sharing therapeutic outcomes, diverge notably in manufacturing, regulation, clinical trials, market entry, and pricing. Original biologics undergo intricate manufacturing processes using living cells or organisms, necessitating extensive clinical trials for regulatory approval, often with global reach. Conversely, biosimilars strive for similarity to the reference biologic while accounting for biological variability, thus following a less rigorous regulatory pathway, including comparative analytical studies and, in some cases, clinical trials. Market dynamics also differ, with original biologics typically protected by patents, leading to higher prices, while biosimilars enter the market post-patent expiry, offering cost savings. Furthermore, while original biologics are prescribed by brand name, biosimilars may gain interchangeable status, enabling pharmacy-level substitution. These distinctions underscore the complex interplay between innovation, regulation, and accessibility in the biopharmaceutical landscape.

CONCLUSION

Biopharmaceuticals are a promising individualized drug approach to treat several disorders in a more targeted manner. In order to produce and use them safely we need to develop good manufacturing practices, better tools to predict unwanted immunogenic responses and adapted formulation development approaches. With emerging technologies, R&D and evolving guidelines for

biologics, a bright future can be foreseen for biopharmaceuticals and we can expect several major new therapies in coming years. With a growing demand for effective and affordable healthcare solutions, there is significant market potential for polymeric biopharmaceuticals in India. Access to these advanced therapies can improve patient outcomes and address unmet medical needs across various therapeutic areas. The status of polymeric biopharmaceuticals in India presents a promising outlook, characterized by ongoing advancements, regulatory advancements, and market potential.

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