



Biosimilar: Opportunity Thrusted over Indian Pharmaceutical Market

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Short Communication

Biosimilar (follow-on biologic or subsequent entry biologic) are biologic products that are highly similar to an already FDA approved biologic product (reference product) manufactured by a company. Biological products are derived from living organisms such as humans, animals and microorganisms through biotechnology, derived from natural sources or produced synthetically. Biologicals are highly valuable for treatment of rheumatoid arthritis, diabetes, anemia, low white blood cell counts, inflammatory bowel disease, multiple sclerosis, psoriasis and various forms of cancer. Some biosimilars consist of small molecules such as human insulin or erythropoietin but mostly are complex molecules such as monoclonal antibodies. Biosimilars exhibit high molecular complexity unlike generic drugs having small molecular structure. Generic drugs are bioequivalent to the brand-name drugs having identical active ingredient and similar safety, quality and performance characteristics for an intended use. Though biosimilars are highly similar to reference product but have allowable differences as derived from living organisms with no clinical differences in terms of safety, purity and potency. Generic small molecule APIs are easy to synthesize and characterize but due to precise nature and function biologicals are very difficult to isolate or synthesize. Biosimilars as new versions of innovator biopharmaceutical products are officially approved based on the similar nature in terms of safety and efficacy to the original "innovator" reference biological products and are only authorized for use once the period of data exclusivity on the original 'reference' biological medicine has expired. The manufacturer submit application for a new biosimilar product with information demonstrating dissimilarity with reference product based on data of analytical, animal and clinical studies [1].

US FDA gave first approval for biosimilar product, Sandoz's Zarxio, a biosimilar version of filgrastim for treatment of neutropenia in 2015, almost 9 years after EU approved launch of Sandoz's human growth hormone Omni trope, the first biosimilar drugs in 2006. Patents on many major biologics has expired in 2016, it's estimated that \$240 billion biosimilar market opportunity is now open for Indian pharmaceuticals industry. This provided an opportunity to Indian pharma companies, active in biotechnology arena, to exploit the world's largest biologics market. Dr Reddy's Laboratories Ltd, is the first Indian firm to rollout with world's first biosimilar antibody with the launch of Reditux (rituximab) in 2007 and now products are currently being sold in over 10 emerging markets. IDEC Pharmaceuticals discovered rituximab and developed the product in collaboration with Genentech, Hoffmann-La Roche and Zenyaku Kogyo of Japan marketed as Rituxan and MabThera. Reditux was launched as a biosimilar version of rituximab at almost half the price of the innovator molecule. Intas Pharmaceuticals launched biosimilar version of rituximab in 2013 named Mabtas and Hetero Drugs, launched its version in 2015, and have led to competitive pricing and greater affordability. Indian companies such as Dr Reddy's, Zydus Cadila, Shantha Biotech/Merieux Alliance, Reliance Life Sciences, Biocon, Wockhardt, Intas are marketing biosimilars in India and other emerging markets. Intas launched the world's first biosimilar version of ranibizumab, used for treating degenerative diseases of the eye. Biocon Ltd, has received approval for insulin glargine in Japan on March 2016 and is gearing up to submit application for approval in Europe and the US for four products. Dr. Reddy's and Zydus Cadila have signed separate agreements with Turkish firms to develop and export biologic products. Biocon formed partnership with Mexican firm Laboratorios PiSA to develop and commercialise biosimilar recombinant human insulin for sale in the US, which can eventually open doors to more affluent tightly regulated UK market. To increase global market reach Indian companies are setting up manufacturing base overseas. Biocon has reportedly invested \$200 million for insulin plant in Malaysia similarly. Cipla is investing about Rs 600 crore for the new biosimilars manufacturing facility in South Africa [2]. The World Health Organization (WHO) has included two newer and more expensive medications, the monoclonal antibodies trastuzumab

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and rituximab in its updated Essential Medicines List (EML) in 2015.

The limitations with biosimilar are that a biosimilars from different origin may have same therapeutic effect but different side-effects requiring thorough testing [3]. Sometimes small change in manufacturing process can cause severe side effects, for example, minor change in the packaging process of Epoetin (Erythropoietin) has reported to cause pure red cell aplasia prompting drug regulatory authorities to establish strict guidelines [4,5]. The Department of Biotechnology and CDSCO has issued 'Guideline on similar biologics: Regulatory Requirements for Marketing Authorization in India' in 2012 for biosimilar drugs outlining specific requirements for pre and post-marketing data for pre-clinical and clinical trials. A revised version of DBT-CDSCO 2012 guideline was launched on 15th Aug 2016 with changes in regulatory steps to implement post-marketing and pharmacovigilance requirement, bring India closer to align with global standards. Aimed at upgrading and maintaining the quality of biosimilar products manufactured in India, CDSCO have given references of ICH regulatory standards so that Indian manufactures can manufacture the biosimilars as per global GMP regulations and can reach out to the world markets like US, Europe, Japan [6]. The Indian guidelines on similar biologics are comparable in many respects to biosimilar guidelines of USA and EU. India has adopted a 'sequential approach' like the 'stepwise approach' of US and EU to market biosimilar products [7]. The Genetic Engineering Approval Committee (GEAC) with the permission of DCGI, approve clinical trials of biosimilar therapeutic products to be conducted in India. The biosimilars are required to demonstrate comparable data on non-clinical studies (pharmacokinetics and toxicology) and clinical studies (efficacy and tolerability for each indication) before it gets approval for all indication of the reference medicine [8].

Geographically, the biosimilars market is dominated by Europe, followed by Asia, North America, followed by other countries of the World. However the Asian market is projected to grow at the highest rate. Key market international players in the biosimilars market are Pfizer Inc. (U.S.), Sandoz International GmbH (Germany), Teva Pharmaceuticals Industries Ltd. (Israel), Amgen Inc. (U.S.), Biocon Ltd. (India), Dr. Reddy's Laboratories Ltd. (India), F. Hoffmann-La Roche Ltd. (Switzerland), Celltrion, Inc. (South Korea), and Samsung Bioepis (South Korea). The biosimilars products are targeted into market segments of oncology, blood disorders, chronic autoimmune diseases, growth hormone deficiency, infectious diseases and other applications. The oncology segment is projected to have the highest market growth during the coming years [9].

India has a thriving biosimilars market for the sheer number of biosimilars available, while Europe has 31 biosimilars on the market and the US has 5, in India there are 66 approved biosimilar products. Biosimilar therapeutic products in India consist primarily of vaccine (Hepatitis B vaccine), monoclonal antibodies, recombinant proteins and diagnostics, insulin, erythropoietin, granulocyte colony stimulating factor, streptokinase, interferon alpha-2B, Rituxinab, epidermal growth factor receptor, chorionic gonadotropin and heparin [10]. Indian pharma companies are now making significant investments into biosimilar development and production in an attempt to secure the early mover advantage and increasingly partnering with western counterparts to launch a greater number of biotherapeutics in both local and international markets. At the same time, innovator companies are gearing up to defend their patents

and market share. In order to preempt such move, Roche teamed up with Emcure Pharmaceuticals to manufacture Herceptin in India after its patent expire in 2013 and sell at a reduced price in under a different name with the intent of maintaining its strong market share. Biocon and Zydus Cadila, are already marketing their biosimilar versions of trastuzumab at less than half the original price in 2014 and 2016 respectively. Roche has taken legal action questioning the similarity and quality claimed by the competitors in legal battles. DCGI considering trastuzumab compulsory license under Section 92 of the 1970 Indian Patent Act, which will authorize manufacture and marketing of low-cost version of the drug without the patent owner's consent to make it more affordable [11].

Though biosimilars have emerged as important tool to treat cancer and autoimmune diseases, they are very highly priced and only used by about 8 percent of patients. US is pushing for setting the exclusivity period of biologic from 12 to 7 years ensure early availability and cost-saving as more companies join the bio-generics race, prices are likely to fall. Indian firms are using differing strategies to sustain in biosimilar market, i.e., some doing in house research while others are attempting to lower risk by taking the licensing route. All countries around the world are now inclined to allow biosimilars and in Indian biogenerics industry is poised with opportunity that happened in case of generics in 1984. India has strong potential to emerge as a key player in the manufacture and marketing of biosimilars with its large consumer base. With the implementation of a new regulatory policy and increased affordability the domestic market is expected to grow at an accelerated pace and reach the target of \$40 billion by 2030 with 20% share in global market. There is need to develop well-designed clinical trial guideline to establish safety and to promote confidence in the new biosimilar products in India. Currently, both manufactures and regulators are strengthening up to meet the future challenges. Biosimilars are the future hope to improve cancer treatment access in low- and middle income group patients.

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