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Review Article

Biologics, biosimilars, intended copies and the era of competitive medicine

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ABSTRACT

Biologics have helped treatment of diseases including cancers, rheumatoid arthritis, etc. in entirely new ways. Because they are expensive, there is a demand for generic versions (biosimilars). Biologicals and biosimilars consist of large complex molecular entities difficult to characterize. An innovator and a biosimilar will never be entirely identical because their manufacturing processes are different; hence both need to be evaluated for potential adverse effects and clinical impact, and thus require a separate regulatory approval process. Biosimilar manufacturing has to follow a similar process as biologics, but may not produce exactly identical result. Hence, there can be variations owing to differences in cell line, transfection and the process in fermentation or purification. Also since biosimilars approval is on limited preclinical and clinical data, it is essential to have a comprehensive post-marketing surveillance to detect safety risks, immunogenic, or adverse reactions. Currently, several products labelled as "biosimilars" are approved in some developing countries, which, at the time of approval, did not have a formal regulatory processes in line with EMA and US-FDA. These products should be considered "intended copies" rather than biosimilars. Physicians should know the difference among biologic, biosimilar, bio-better and an 'intended copy' to make an informed prescribing decision or substitution.

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1. Development of biosimilars

1.1. *Definition of biosimilars*

Biotechnology has revolutionized the way diseases are treated. Recombinant DNA technology has allowed the development of bio-pharmaceuticals, which can mimic the complex body proteins. These unique agents have helped the treatment of diseases in entirely new ways. Biotechnology-derived drugs are called biologics[1] which today have become an essential part of modern pharmacotherapy.[2]

The ability to produce biologics has resulted in an improved understanding of mechanisms of diseases and resulted in the development of a plethora of innovative drugs and vaccines that have improved outcomes in the areas of un-met clinical needs, including cancers, rheumatoid arthritis, Crohn's disease, multiple sclerosis, macular degeneration, retinal vein occlusions, psoriatic skin diseases and Gaucher disease.[3,4] Today several biologics have entered into the global market of pharmaceuticals.[5] These include biosynthetic monoclonal antibodies, insulins, peptide hormones and analogues, haematopoietic and non-haematopoietic growth factors, interferons, interleukins, erythropoietins, fusion proteins, 'recombinantly produced antigens' (vaccines) and other innovative products that account for a substantial portion of all human medicines.[5,6] It is an astonishing fact that one third of new medical entities launched are biologics.[7]

Globally the sale of biologics was approximately $142 billion in 2011.[8] Global Industries Analysts have forecasted that the market for biologics would be $158 billion by 2015.[9] Approximately, 30% of the pharmaceutical and biotech industries pipeline is composed of biologics, and it is anticipated that by 2016 ten of 20 top selling drugs will be biologics.[10] Presently biologics, including Humira (Adalimumab), Enbrel (Etanercept), Remicade (Infliximab), Avastin (Bevacizumab), Lantus (Insulin Glargine), Rituxan (Rituximab), Herceptin (Trastuzumab), Prolia (Denosumab) and Lucentis (Ranibizumab), are among the top selling pharmaceuticals worldwide.[3]

Though biologics are highly effective, life-altering therapies, yet they are expensive and often prescribed long-term for chronic medical conditions. This imposes a burden either on national health care systems or on the patients' pocket.[10,11]

Hence, there is a natural demand for generic cheaper versions of these drugs. The patents of many first generation biologics developed in 1980s and 1990s have started to expire and there is a growing market demand for generic versions of these innovators called bio-similars. The terminology 'biosimilar' is used in accordance with the fact that second generation biologics cannot be exactly the same as innovators owing to structural and manufacturing complexities of biopharmaceuticals, making them similar but not exactly same as in the case of less complex small molecule pharma drugs.

In principle, biosimilars are the biologic medicines' equivalent of chemical generics and have a similar active component. However, biologicals and biosimilars are manufactured from living cells or organisms and consist of relatively large and often highly complex molecular entities that may be difficult to fully characterize. Even among different batches of the same biologic, there would be variability, because the manufacturing process is complex, besides the inherent variability of the biologic system.[12] As the way these molecules are manufactured is different, an innovator and a biosimilar will never be entirely identical. Differences would need to be evaluated for potential adverse effects and impact on the clinical performance of the biosimilar. These reasons mandate a separate regulatory and license approval for biosimilars.[13]

Different countries have established legal and regulatory pathways for bringing in biosimilars to the market. The regulatory body for the European Union (EMEA) and US (US-FDA) have developed guidelines for the approval of manufacture and sale of biosimilars. A variety of terms, such as 'biosimilar products', 'follow-on protein products' and 'subsequent-entry biologics' have been coined by different jurisdictions to describe these products.[14]

The European Union was the first region in the world to have set up a legal framework and a regulatory pathway for biosimilars.[15]

The EMEA defined biosimilars as 'A biological medicine that is developed to be similar to an existing biological medicine. When approved for use, any differences between it and its reference medicine will have been shown not to affect safety or effectiveness'.[16] US-FDA defined biosimilars as 'A biological product that is highly similar to a US licensed reference biological product notwithstanding 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'.[17] The Australian Therapeutic Goods Administration as well as the Canadian health authorities biosimilar guidance document is based on European guidelines.[17]

World Health Organization defined biosimilars as 'A biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product'. Biosimilars have to depend on the efficacy and safety data of innovators for their licensing.[14]

1.2. *Rationale for development*

The biosimilar market is expanding rapidly and the main incentives for driving the development of biosimilars are quite the same as those for developing small molecular weight chemical 'generic' drugs.[5] Key factors driving market growth include availability of new innovative technology, to promote market competition, patent expiries of key biological drugs, produce efficient and safe medicines at affordable prices, cost containment measures from governments, meet the worldwide demand and the increasing ageing population globally.[5]

1.3. *The 'Patent Cliff'*

Since early 1980s biologics have revolutionized the treatment of many diseases. But as the patents and data protection measures expired or are nearing expiration, considerable interest has turned to making biosimilars.[18] This expiration of a 20 year exclusivity period for a lot of biologics, has given rise to the ''patent cliff'' (clustering of patent expirations of numerous biologics occurring between 2011 and 2019) (Table 1). This